

Martindale

The Complete Drug Reference

Thirty-seventh edition

Edited by

Sean C Sweetman

BPharm, FRPharmS


London • Chicago **Pharmaceutical Press**

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RS141.3
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2011
V. 1

Published by Pharmaceutical Press

1 Lambeth High Street, London SE1 7JN, UK
1559 St. Paul Avenue, Gurnee, IL 60031, USA

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(PP) is a trade mark of Pharmaceutical Press

Pharmaceutical Press is the publishing division of the Royal Pharmaceutical Society of Great Britain

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

Thirty-seventh edition published 2011

Printed in Italy by LEGO S.p.A.

ISBN 978 0 85369 933 0

ISSN 0263-5364

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The book should be interpreted in light of professional knowledge and supplemented as necessary by specialised publications and product literature. The reader should ensure that the information being used is consistent with normal, generally accepted healthcare practice.

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

Preface

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

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

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

As always the contents have been extensively revised, with all the text scanned and revalidated where necessary by a team of experienced pharmacists. Over 240 monographs have been added, and 171 removed from the book (abbreviated information on the latter remains available in the electronic versions). In our continuing attempts to improve the usefulness of the book, the chapters on Colouring Agents, Nonionic Surfactants, Organic Solvents, Paraffins and Similar Bases, Soaps and Other Anionic Surfactants, and Stabilising and Suspending Agents have been amalgamated and with additional material now form the new chapter Pharmaceutical Excipients.

The disease treatment reviews, 675 in all and generally located in the chapter introductions, have also been revised in order to reflect current trends and provide key references. Cross-references to these reviews appear in the monographs of the drugs cited; the reviews can also be accessed via the general index. It is hoped that these reviews will be of use to readers who want an overview of a particular disease and its drug treatment and will provide a useful starting point for those who want to pursue particular aspects further.

Martindale contains much nomenclature information intended to assist the reader in identifying a particular drug or compound, and for this edition we have again greatly expanded our coverage of synonyms, with increased coverage of Russian synonyms and 'street names' for substances of abuse. Coverage of ATC codes has been expanded to include codes assigned to herbal medicines. This edition also carries for the first time the unique ingredient identifiers (UNIs) that are generated by the joint FDA/USP Substance Registration System.

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

The information on proprietary preparations, an important feature of Martindale, has been updated and the number of countries covered has again been increased. For this edition homeopathic proprietary preparations have also been listed at the end of the relevant monographs according to their ingredients.

Martindale is based on published information and more than 54 500 selected references are included. The amount of drug information now published electronically has increased significantly since the last printed edition of Martindale and this edition now includes over 3400 citations to material available on the Internet as web pages. Because of the nature of the Internet, there is no way to guarantee that the material referred to by a URL will remain at that location, as many sites are subject to periodic reorganisation; additionally, the content of Internet documents may change without warning. All URLs in Martindale are rechecked shortly before publication to ensure that a document is present. The accession date given in the citation represents the last date on which the content of the document was referred to during revalidation.

Our objective is to evaluate the literature, covering important studies, guidelines, and useful reviews and placing them in context. Multicentre studies, meta-analyses, and systematic reviews play an important role in the study of drug treatment, and their findings and conclusions are considered in many of our chapters. However, there is also a place for the anecdotal report and the small study, and information from such sources is included where appropriate. In compiling the text of a Martindale monograph extensive use is made of the drug's licensed product information as published in various countries and

approved by the relevant regulatory health bodies. Acknowledgement is also given to information referenced from a number of authoritative sources including the *British National Formulary*, the *British National Formulary for Children*, the *British Pharmacopoeia*, the *European Pharmacopoeia*, the *United States National Formulary*, and the *United States Pharmacopoeia*.

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

Philosophy and methodology

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

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

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

MARTINDALE STAFF. Martindale is currently produced by a team of 21 people, 18 of whom are pharmacists or pharmacy technicians with relevant expertise. The team is divided into 5 revising groups each of 2 or 3 staff editors, as well as 5 assistant editors, 1 editor-in-chief, a co-ordinator for the processing of information on proprietary medicines, and 3 clerical and support staff. A number of pharmacists work as external evaluators to maintain coverage of non-UK preparations.

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

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

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

PROPRIETARY PREPARATIONS. The Martindale proprietary preparations team evaluate licensed product information for 41 countries and regions, in order to maintain the widest possible coverage of drugs in use internationally. Preparation names, manufacturers, ingredients, and licensed uses are included in the internal Martindale database for review during the revision process, and any significant additional information is forwarded to the relevant revision team.

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

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

EDITING. The chapter is then passed to a member of the senior editorial staff, who performs a second check and preliminary editing of the data. This process

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

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

ADDITIONAL CHECKS FOR PUBLICATION. Some additional checks are made before publishing a print edition of Martindale. A second independent dose check of all chapters is made by an external expert, all cross-references are revalidated, and tests of the typesetting and page structure are made. In addition our extensive index is generated and carefully checked for accuracy, order, and consistency. All URLs are also rechecked at this stage to ensure that they still link to the material cited.

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

Arrangement

VOLUME A: • MONOGRAPHS ON DRUGS AND ANCILLARY SUBSTANCES (pages 1–2658). This section contains 5930 monographs arranged in 49 chapters. These chapters generally bring together monographs on drugs and groups of drugs that have similar uses or actions. The introductions of those chapters that describe drugs used in the management of disease may contain disease treatment reviews—descriptions of those diseases together with reviews of the choice of treatments. The last chapter in this section consists of a series of monographs arranged in the alphabetical order of their main titles. It includes monographs on drugs not easily classified, on herbals, and on drugs no longer used clinically but still of interest. There are also monographs on toxic substances, the effects of which may require drug therapy.

VOLUME B: • PREPARATIONS (pages 2659–3554). This section contains over 161 700 proprietary preparations from a range of countries and regions. For this edition we have covered Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Indonesia, Ireland, Israel, Italy, Malaysia, Mexico, the Netherlands, New Zealand, Norway, Philippines, Poland, Portugal, Russia, Singapore, South Africa, Spain, Sweden, Switzerland, Thailand, Turkey, Ukraine, the United Arab Emirates, UK, USA, and Venezuela. We have also included some proprietary preparations from Japan. The information provided includes the proprietary name, the manufacturer or distributor, the active ingredients with cross-references to the drug monographs, and a summary of the indications as given by the manufacturer.

- **DIRECTORY OF MANUFACTURERS** (pages 3555–3636). In Martindale the names of manufacturers and distributors are abbreviated. Their full names are given in this directory together with the full address and website if it is available. This directory contains about 15 300 entries.

- **MULTILINGUAL PHARMACEUTICAL TERMS** (pages 3637–3656). This index lists nearly 5600 of the commoner pharmaceutical forms and routes in 13 major European languages. It is provided as an aid to the non-native speaker in interpreting packaging, product information, or prescriptions written in another language.

- **GENERAL INDEX** (pages 3657–4112). To make fullest use of the contents of Martindale the general index should always be consulted. The exhaustive index, prepared from 172 000 entries, includes entries for drugs (approved names, synonyms, and chemical names), preparations, pharmacological and therapeutic groups, and clinical uses (disease treatment reviews). As in previous editions, the index is arranged alphabetically 'word-by-word' rather than 'letter-by-letter'. The index indicates the column in which the relevant entry appears as well as the

page and in which volume the entry may be found. To improve clarity and the ease of location of index entries long chemical names have been omitted from the index.

- **CYRILLIC INDEX** (pages 4113–4147). Both nonproprietary and proprietary names in Russian may be found in Russian alphabetical order in this section.

Nomenclature

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

Graphical representations of the chemical structures for over 4100 of the drugs are also included.

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

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

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

UNII CODES. The unique ingredient identifiers, which are generated by the joint FDA/USP Substance Registration System have been provided, where available. Numbers for various forms of the monograph or related substances are listed with the variation in form given in parentheses.

Atomic and Molecular Weights

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

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Pharmacopoeias

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

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

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

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

Pharmaceutical Information

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

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

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

solubility

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

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

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

Drugs in Sport

Wherever possible we have attempted to indicate those drugs and substances that may be subject to restriction in some or all sports, either in their own right, or because they are a derivative of a restricted substance or a member of a prohibited group. Proprietary preparations containing such compounds are also marked in the preparation section in Volume B. The definitive guide used for identifying restricted drugs for this edition is the 2010 Prohibited List issued by the World Anti-Doping Agency (WADA—see www.wada-ama.org). However, these regulations, which are issued annually, are subject to interpretation and therapeutic exemption, and may vary from sport to sport; particular sporting authorities may also issue additional restrictions, and competitors should always

check with the appropriate body. The rules are constantly evolving and the absence of any indication of restriction in Martindale should not be taken as absolute confirmation that the substance may legitimately be taken by a competitor.

Pharmacological and Therapeutic Information

Information on adverse effects, treatment of adverse effects, precautions (including contra-indications), interactions, pharmacokinetics, and uses and administration of each substance is provided by concise statements and these may be elaborated and expanded by referenced reviews and abstracts from papers and other publications. This edition contains over 16 400 such abstracts or reviews based on information in an ever widening range of publications.

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

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

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

Doses

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

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

Acknowledgements

The Editor gratefully acknowledges the advice and assistance of the many experts who have suggested amendments to the text of Martindale. Thanks are also due to Osquel Barroso, Karen Baxter, Lina Bladh, Thomas Brendler, Larry Callahan, Alessandro Gabbi, Judy van Engeldorp Gastelaars, Špela Godec, Jan Horn, Montserrat Jané, Andrius Kairys, Maria Kouimtz, Rhoda Lee, Dinesh Mehta, Carla Oliveira, Frank Post, Anne Prasad, Olivier Rabin, Kamila Ramešová, Elsa Simon, Gyöngyver Soós, Carina Tukukino, Robert Wasilewski, Frank Switzer, and Paul Weller, for advice and comments on specific issues during revision. The Editor is grateful to the many organisations that have helped in providing information.

Martindale staff have been able to call on the expertise of other members of the Royal Pharmaceutical Society's staff. In particular the Editor is grateful to John Martin and the staff of the British National Formulary, and the staff of the library and information department. Thanks are due to Ian Baxter, Mildred Davis, Sam Driver, Marian Fenton, Eileen Laughton, Rosalind McLamey, Claire Norton, James O'Reilly, and Susan Shankie for their editorial tasks. Thanks are also due to Bob Bolick and the staff of the Pharmaceutical Press for their support.

The contents of this 37th edition were planned, written, checked, indexed, keyed, proofed, and processed by the Martindale staff. The Editor is pleased to acknowledge the skills and commitment of all the Martindale staff and to record his gratitude: to Christine Iskandar for clerical assistance; to Chloë Hatwal and Elizabeth King for editorial assistance; to the Staff Editors Catherine Cadart, Kathleen Eager, Austin Gibbons, Sue Handy, Fauziah Hashmi, Sue Ho, Joanna Humm, Kelli Kalb, Jean Macpherson, Priya Patel, Sandra Sutton, and Gerda Viedge; to the Assistant Editors Alison Brayfield, Julie McGlashan, Gail Neathercoat, and Anne Parsons; and to the Senior Assistant Editor Paul Blake.

London October 2010

Abbreviations

For abbreviations of the names of manufacturers or their distributors, see Directory of Manufacturers, page 3555.

ACE—angiotensin-converting enzyme.
ADHD—attention deficit hyperactivity disorder.
agg.—aggregate (in botanical names), including 2 or more species which resemble each other closely.
AIDS—acquired immunodeficiency syndrome.
a.m.—*ante meridiem*, ‘before noon’.
ARC—AIDS-related complex.
Arg.—Argentina.
ATC—Anatomical Therapeutic Chemical classification.
AUC—area under the concentration-time curve.
Austral.—Australia.
AV—atrioventricular.
BAN—British Approved Name.
BANM—British Approved Name Modified.
Belg.—Belgium.
BMA—British Medical Association.
BMI—body mass index.
BNF—British National Formulary.
BNFC—British National Formulary for Children.
b.p.—boiling point.
BP—British Pharmacopoeia. Unless otherwise specified, BP references are to the 2010 edition.
BP(Vet)—British Pharmacopoeia (Veterinary) 2010.
BPC—British Pharmaceutical Codex.
Br.—British.
Braz.—Brazil.
Bulg.—Bulgaria.
BUN—Blood-urea-nitrogen.
°C—degrees Celsius (centigrade). Unless otherwise indicated in the text, temperatures are expressed in this thermometric scale.
Canad.—Canada.
CAPD—continuous ambulatory peritoneal dialysis.
CAS—Chemical Abstracts Service.
CCPD—continuous cycle peritoneal dialysis.
CDC—Centers for Disease Control and Prevention (USA) (formerly Centers for Disease Control).
Chin. P.—Chinese Pharmacopoeia 2005.
CHM—Commission on Human Medicines (UK).
CI—Colour Index.
CMV—cytomegalovirus.
CNS—central nervous system.
cP—centipoise(s).
CPMP—Committee on Proprietary Medicinal Products of the European Union.
cs—Czech.
CSF—cerebrospinal fluid.
CSM—Committee on Safety of Medicines (UK) (now subsumed within the Commission on Human Medicines).
cSt—centistokes.
Cz.—Czech Republic.
D & C—designation applied in USA to dyes permitted for use in drugs and cosmetics.

de—German.
d.c.—direct current.
DEFRA—Department for Environment, Food, and Rural Affairs (UK).
Denm.—Denmark.
DHSS—the former Department of Health and Social Security (UK).
dL—decilitre(s).
DNA—deoxyribonucleic acid.
DoH—Department of Health (UK).
DTF—Drug Tariff Formulary.
ECG—electrocardiogram.
ECT—electroconvulsive therapy.
Ecuad.—Ecuador.
ed.—editor(s) *or* edited by *or* edition.
EEC—European Economic Community, now the European Union.
EEG—electro-encephalogram.
e.g.—*exempli gratia* ‘for example’.
el—Greek.
EMEA—European Medicines Agency.
ENL—erythema nodosum leprosum.
es—Spanish.
ESRD—end-stage renal disease.
et al.—*et alii*, ‘and others’: for three or more co-authors or co-workers.
et seq.—and what follows.
EU—European Union.
Eur. P.—see Ph. Eur.
Ext. D & C—designation applied in USA to dyes permitted for use in external drug and cosmetic preparations.
°F—degrees Fahrenheit.
FAC—Food Additives and Contaminants Committee of the former Ministry of Agriculture, Fisheries and Food (UK).
FAO—Food and Agriculture Organization of the United Nations.
FAO/WHO—Food and Agriculture Organization of the United Nations and the World Health Organization.
FDA—Food and Drug Administration of USA.
FdAC—Food Advisory Committee of the former Ministry of Agriculture, Fisheries and Food (UK).
FD & C—designation applied in USA to dyes permitted for use in foods, drugs, and cosmetics.
FEV₁—forced expiratory volume in 1 second.
Fin.—Finland.
FIP—Fédération Internationale Pharmaceutique.
f.p.—freezing point.
FPA—Family Planning Association (UK).
fr—French.
Fr.—France.
Fr. P.—French Pharmacopoeia 1982 (Pharmacopée Française, X^e Edition) and updates up to 2003.
g—gram(s).
Ger.—Germany.
Ger. P.—German Pharmacopoeia (Deutsches Arzneibuch, 2007).
GFR—glomerular filtration rate.
G6PD—glucose-6-phosphate dehydrogenase.
Gr.—Greece.
HAART—highly active antiretroviral therapy.

- Hb**—haemoglobin.
- Hib**—*Haemophilus influenzae* type b.
- HIV**—human immunodeficiency virus.
- HLA**—human lymphocyte antigens.
- HLB**—hydrophilic-lipophilic balance.
- HRT**—hormone replacement therapy.
- HSE**—Health and Safety Executive (UK).
- hu**—Hungarian.
- Hung.**—Hungary.
- IARC**—International Agency for Research on Cancer.
- ibid.**—*ibidem*, ‘in the same place (journal or book)’.
- idem**—‘the same’: used for the same authors and titles.
- i.e.**—*id est*, ‘that is’.
- Ig**—immunoglobulin.
- Indon.**—Indonesia.
- INN**—International Nonproprietary Name.
- INN^M**—International Nonproprietary Name Modified.
- Int. P.**—International Pharmacopoeia 4th ed., 2006, and Supplement 1, 2008.
- IPCS**—International Programme on Chemical Safety.
- IQ**—intelligence quotient.
- IrI.**—Ireland.
- ISH**—International Society of Hypertension.
- it**—Italian.
- It. P.**—Italian Pharmacopoeia 11th ed., 2002 (Farmacopea Ufficiale della Repubblica Italiana, XI Edizione, 2002).
- Ital.**—Italy.
- IUD**—intra-uterine device.
- IUPAC**—International Union of Pure and Applied Chemistry.
- IVF**—*in-vitro* fertilisation.
- J**—joule(s).
- Jpn**—Japan.
- Jpn P.**—The Pharmacopoeia of Japan, 15th ed., 2006 and Supplement 1.
- K**—kelvin.
- kcal**—kilocalorie(s).
- kg**—kilogram(s).
- kJ**—kilojoule(s).
- lb**—pound(s) avoirdupois.
- LD₅₀**—a dose lethal to 50% of the specified animals or micro-organisms.
- Lf**—limes flocculation.
- lt**—Lithuanian.
- m**—metre(s).
- m²**—square metre(s).
- m³**—cubic metre(s).
- M**—molar.
- MAFF**—the former Ministry of Agriculture, Fisheries and Food (UK), now Department of Environment, Food, and Rural Affairs (DEFRA).
- MAOI**—monoamine oxidase inhibitor.
- max.**—maximum.
- MBC**—minimum bactericidal concentration.
- MCA**—Medicines Control Agency, now MHRA (UK).
- mEq**—milliequivalent(s).
- Mex.**—Mexico.
- mg**—milligram(s).
- MHRA**—Medicines and Healthcare products Regulatory Agency (UK).
- MIC**—minimum inhibitory concentration.
- min**—minute.
- min.**—minimum.
- MJ**—megajoule(s).
- mL**—millilitre(s).
- mm**—millimetre(s).
- mm²**—square millimetre(s).
- mm³**—cubic millimetre(s).
- mmHg**—millimetre(s) of mercury.
- mmol**—millimole.
- mol**—mole.
- mol. wt**—molecular weight.
- Mon.**—Monaco.
- mosmol**—milliosmole.
- m.p.**—melting point.
- MRC**—Medical Research Council (UK).
- MRSA**—meticillin-resistant *Staphylococcus aureus*.
- µg**—microgram(s).
- µm**—micrometre(s).
- N**—normal.
- n.b.**—*nota bene*, note carefully.
- Neth.**—The Netherlands.
- NICE**—National Institute for Health and Clinical Excellence (formerly the National Institute for Clinical Excellence) (UK).
- NIH**—National Institutes of Health (USA).
- nl**—Dutch.
- nm**—nanometre(s).
- NMDA**—*N*-methyl-D-aspartate.
- NNRTI**—non-nucleoside reverse transcriptase inhibitor.
- Norw.**—Norway.
- NRTI**—nucleoside reverse transcriptase inhibitor.
- NSAID**—nonsteroidal anti-inflammatory drug.
- NYHA**—New York Heart Association.
- NZ**—New Zealand.
- OP**—over proof.
- o/w**—oil-in-water.
- P**—probability.
- Pa**—pascal(s).
- Pak.**—Pakistan.
- pCO₂**—plasma partial pressure (concentration) of carbon dioxide.
- p_aCO₂**—arterial plasma partial pressure (concentration) of carbon dioxide.
- PEN**—Pharmacy Equivalent Name, see page vi.
- pg**—picogram(s).
- pH**—the negative logarithm of the hydrogen ion concentration.
- Ph. Eur.**—European Pharmacopoeia, 6th ed., 2008 and Supplements 6.1 to 6.8.
- Pharm. Soc. Lab. Rep.**—Royal Pharmaceutical Society’s Laboratory Report.
- Philipp.**—Philippines.
- PHLS**—Public Health Laboratory Service (UK).
- pINN**—Proposed International Nonproprietary Name.
- pINN^M**—Proposed International Nonproprietary Name Modified.
- pK_a**—the negative logarithm of the dissociation constant.
- pl**—Polish.
- p.m.**—*post meridiem*, ‘afternoon’.
- pO₂**—plasma partial pressure (concentration) of oxygen.
- p_aO₂**—arterial plasma partial pressure (concentration) of oxygen.
- Pol.**—Poland.
- Pol. P.**—Polish Pharmacopoeia 6th ed., 2002 (Farmakopea Polska VI, 2002) and Supplement 2005.
- Port.**—Portugal.
- ppm**—parts per million.
- PSGB**—The Pharmaceutical Society of Great Britain. Now the Royal

Pharmaceutical Society.

pt—Portuguese.

PUVA—psoralen with UVA light irradiation.

PVC—polyvinyl chloride.

RCGP—Royal College of General Practitioners (UK).

RIMA—reversible inhibitor of monoamine oxidase type A.

rINN—Recommended International Nonproprietary Name.

rINN**M**—Recommended International Nonproprietary Name Modified.

RNA—ribonucleic acid.

RPSGB—The Royal Pharmaceutical Society of Great Britain. Now the Royal Pharmaceutical Society

RSV—respiratory syncytial virus.

Rus.—Russia.

S. Afr.—South Africa.

SGOT—serum glutamic oxaloacetic transaminase (serum aspartate aminotransferase *now preferred*).

SGPT—serum glutamic pyruvic transaminase (serum alanine aminotransferase *now preferred*).

SI—Statutory Instrument *or* Système International d'Unités (International System of Units).

sic—written exactly as it appears in the original.

SLE—systemic lupus erythematosus.

sp.—species (plural spp.).

sp. gr.—specific gravity.

Span.—Spanish.

Span. P.—Spanish Pharmacopoeia 2nd ed., 2002 (Real Farmacopoea Española, Segunda Edición, 2002) and Supplement 2.1.

SSRI—selective serotonin reuptake inhibitor.

St—stokes.

subsp.—subspecies.

suppl—supplement(s).

sv—Swedish.

Swed.—Sweden.

Swiss P.—Swiss Pharmacopoeia 2006 (Pharmacopoea Helvetica, 10 Ausgabe, Deutsche Ausgabe).

Switz.—Switzerland.

Thai.—Thailand.

TNF—tumour necrosis factor.

THM—traditional herbal medicine.

THMP—traditional herbal medicinal product.

TPN—total parenteral nutrition.

Turk.—Turkey.

UAE—United Arab Emirates.

UK—United Kingdom.

Ukr.—Ukraine.

UNICEF—United Nations Children's Fund.

UP—under proof.

Urug.—Uruguay.

US and **USA**—United States of America.

USAN—United States Adopted Name.

USNF—The United States 'National Formulary 28', 2010, and Supplement 1.

USP—The United States Pharmacopeia 33, 2010, and Supplement 1.

UV—ultraviolet.

var.—variety.

Venez.—Venezuela.

Viet.—Vietnamese.

Viet. P.—Vietnamese Pharmacopoeia 2002 (Pharmacopoeia Vietnamica, Editio III).

vol.—volume(s).

v/v—volume in volume.

v/w—volume in weight.

WHO—World Health Organization.

w/o—water-in-oil.

wt—weight.

wt per mL—weight per millilitre.

w/v—weight in volume.

w/w—weight in weight.

Preparations

Proprietary Preparations (details are given in Volume B)

Arg.: Anidra; **Austral.:** Anidra; **Austria:** Anidra; **Belg.:** Anidra; **Braz.:** Anidra; **Canada:** Anidra; **Chile:** Anidra; **Cz.:** Anidra; **Denm.:** Anidra; **Fin.:** Anidra; **Fr.:** Anidra; **Ger.:** Anidra; **Gr.:** Anidra; **Hong Kong:** Anidra; **India:** Anidra; **Indon.:** Anidra; **Ir.:** Anidra; **Israel:** Anidra; **Italy:** Anidra; **Malaysia:** Anidra; **Mex.:** Anidra; **Neth.:** Anidra; **Qatar:** Anidra; **Norw.:** Anidra; **Philipp.:** Anidra; **Pol.:** Anidra; **Port.:** Anidra; **Qatar:** Anidra; **Rus.:** Anidra; **S. Afr.:** Anidra; **Singapore:** Anidra; **Spain:** Anidra; **Swed.:** Anidra; **Switz.:** Anidra; **Thai.:** Anidra; **Turk.:** Anidra; **UK:** Anidra; **Ukr.:** Anidra (Аридрат); **USA:** Anidra.

Fosinopril Sodium (BANM, USAN, rINN)

Fosinoprilnatrium; Fosinopril sódico; Fosinopril sodique; Fosinopril Sodium; Fosinoprilnatrium; Fosinoprilum natrium; Natrii Fosinoprilum; SQ-28555. (4S)-4-Cyclohexyl-1-[[[(R)-2-methyl-1-(propionyloxy)propoxy]-[4-phenylbutyl]phosphinyloxy]acetyl]-L-proline sodium.

Натрий Фозиноприл

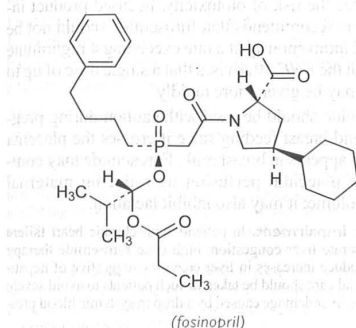
$C_{30}H_{45}NNaO_7P = 585.6$

CAS — 97825-24-6 (fosinopril); 98048-97-6 (fosinopril); 88889-14-9 (fosinopril sodium).

ATC — C09AA09.

ATC Vet — QC09AA09.

UNII — NW2RTH6T2N.



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

Ph. Eur. 6.8 (Fosinopril Sodium). A white or almost white, crystalline powder. It shows polymorphism. Freely soluble in water; sparingly soluble in dehydrated alcohol; practically insoluble in hexane.

USP 33 (Fosinopril Sodium). Store in airtight containers at a temperature of 20° to 25°, excursions permitted between 15° and 30°.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p.1315.

Interactions

As for ACE inhibitors, p.1318.

Pharmacokinetics

Fosinopril acts as a prodrug of the diacid fosinoprilat, its active metabolite. About 36% of an oral dose of fosinopril is absorbed. Fosinopril is rapidly and completely hydrolysed to fosinoprilat in both gastrointestinal mucosa and liver. Peak plasma concentrations of fosinoprilat occur about 3 hours after an oral dose of fosinopril. Fosinoprilat is more than 95% bound to plasma proteins. It is excreted both in urine and in the faeces via the bile; it has been detected in breast milk. The effective half-life for accumulation of fosinoprilat after multiple doses of fosinopril is about 11.5 hours in patients with hypertension and about 14 hours in patients with heart failure.

References

1. Singhi SM, *et al.* Disposition of fosinopril sodium in healthy subjects. *Br J Clin Pharmacol* 1988; 25: 9-15.
2. Kostis JB, *et al.* Fosinopril: pharmacokinetics and pharmacodynamics in congestive heart failure. *Clin Pharmacol Ther* 1995; 58: 660-5.

Renal impairment. Total body clearance of fosinoprilat, the active metabolite of fosinopril, is slower in patients with renal impairment. However, pharmacokinetic studies in patients with

varying degrees of impairment,¹⁻⁵ including those requiring dialysis, indicate that decreases in renal clearance may be compensated for, at least in part, by increases in hepatic clearance.

1. Hui KK, *et al.* Pharmacokinetics of fosinopril in patients with various degrees of renal function. *Clin Pharmacol Ther* 1991; 49: 457-67.
2. Gehr TWB, *et al.* Fosinopril pharmacokinetics and pharmacodynamics in chronic ambulatory peritoneal dialysis patients. *Eur J Clin Pharmacol* 1991; 41: 165-9.
3. Sica DA, *et al.* Comparison of the steady-state pharmacokinetics of fosinopril, lisinopril and enalapril in patients with chronic renal insufficiency. *Clin Pharmacokinet* 1991; 20: 420-7.
4. Gehr TWB, *et al.* The pharmacokinetics and pharmacodynamics of fosinopril in haemodialysis patients. *Eur J Clin Pharmacol* 1993; 45: 431-6.
5. Greenbaum R, *et al.* Comparison of the pharmacokinetics of fosinoprilat with enalaprilat and lisinopril in patients with congestive heart failure and chronic renal insufficiency. *Br J Clin Pharmacol* 2000; 49: 23-31.

Uses and Administration

Fosinopril is an ACE inhibitor (p.1315). It is used in the treatment of hypertension (p.1290) and heart failure (p.1284).

Fosinopril owes its activity to fosinoprilat to which it is converted after oral doses. The haemodynamic effects are seen within 1 hour of a single oral dose and the maximum effect occurs after 2 to 6 hours, although the full effect may not develop for several weeks during chronic dosing. The haemodynamic action lasts for about 24 hours, allowing once-daily dosing. Fosinopril is given orally as the sodium salt.

In the treatment of **hypertension**, the initial dose of fosinopril sodium is 10 mg once daily. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. Usual maintenance doses range from 10 to 40 mg once daily. In patients already taking diuretic therapy the diuretic should be withdrawn if possible several days before starting fosinopril, and resumed later if necessary.

In the management of **heart failure**, severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus treatment should begin with a low dose under close medical supervision. Fosinopril sodium is given in an initial dose of 10 mg once daily and, if well tolerated, increased to a maximum of 40 mg once daily. An initial dose of 5 mg may be given in patients at high risk of hypotension.

For doses in children, see below.

References

1. Murdoch D, McTavish D. Fosinopril: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in essential hypertension. *Drugs* 1992; 43: 123-40.
2. Wagstaff AJ, *et al.* Fosinopril: a reappraisal of its pharmacology and therapeutic efficacy in essential hypertension. *Drugs* 1996; 51: 777-91.
3. Davis R, *et al.* Fosinopril: a review of its pharmacology and clinical efficacy in the management of heart failure. *Drugs* 1997; 54: 103-16.

Administration in children. US licensed product information recommends that fosinopril sodium may be given to children weighing over 50 kg in the treatment of hypertension in an oral dose of 5 to 10 mg once daily.

Preparations

USP 33: Fosinopril Sodium and Hydrochlorothiazide Tablets; Fosinopril Sodium Tablets.

Proprietary Preparations (details are given in Volume B)

Austral.: Fosipril; **Monac.:** Monopril; **Austria:** Fositen; **Belg.:** Fosinil; **Braz.:** Monopril; **Canada:** Anidra; **Chile:** Monopril; **Cz.:** Apo-Fosinopril; **Denm.:** Fosinopril; **Fin.:** Fosinopril; **Fr.:** Fosinopril; **Ger.:** Fosinopril; **Gr.:** Fosinopril; **Hong Kong:** Fosinopril; **India:** Fosinopril; **Indon.:** Fosinopril; **Ir.:** Fosinopril; **Israel:** Fosinopril; **Italy:** Fosinopril; **Malaysia:** Fosinopril; **Mex.:** Fosinopril; **Neth.:** Fosinopril; **Philipp.:** Fosinopril; **Pol.:** Fosinopril; **Port.:** Fosinopril; **Rus.:** Fosinopril (Фозинар); **S. Afr.:** Fosinopril; **Singapore:** Fosinopril; **Spain:** Fosinopril; **Swed.:** Fosinopril; **Switz.:** Fosinopril; **Thai.:** Fosinopril; **Turk.:** Fosinopril; **UAE:** Fosinopril; **UK:** Fosinopril; **Ukr.:** Fosinopril (Фозинар); **USA:** Fosinopril; **Venez.:** Fosinopril.

Multi-ingredient: **Austral.:** Fosicet; **Belg.:** Fosicet; **Braz.:** Fosicet; **Chile:** Fosicet; **Cz.:** Fosinopril Plus H; **Fr.:** Fosicet; **Gr.:** Fosinopril Plus; **Hong Kong:** Fosinopril Plus; **India:** Fosinopril Plus; **Indon.:** Fosinopril Plus; **Ir.:** Fosinopril Plus; **Israel:** Fosinopril Plus; **Italy:** Fosinopril Plus; **Malaysia:** Fosinopril Plus; **Mex.:** Fosinopril Plus; **Neth.:** Fosinopril Plus; **Philipp.:** Fosinopril Plus; **Pol.:** Fosinopril Plus; **Port.:** Fosinopril Plus; **Rus.:** Fosinopril Plus (Фозинар Плюс); **S. Afr.:** Fosinopril Plus; **Singapore:** Fosinopril Plus; **Spain:** Fosinopril Plus; **Swed.:** Fosinopril Plus; **Switz.:** Fosinopril Plus; **Thai.:** Fosinopril Plus; **Turk.:** Fosinopril Plus; **UAE:** Fosinopril Plus; **UK:** Fosinopril Plus; **Ukr.:** Fosinopril Plus; **USA:** Fosinopril Plus; **Venez.:** Fosinopril Plus.

Furosemide (BAN, USAN, rINN) ⊗

Furosemide; Furosemid; Furosemida; Furosemide; Furosemid; Furosemidum; Furosemid; Furozemid; Furozemidas; LB-502. 4-Chloro-N-furfuryl-5-sulphamoylanthranilic acid.

Фуросемид

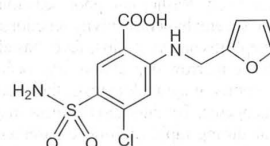
$C_{12}H_{11}ClN_2O_5S = 330.7$

CAS — 54-31-9.

ATC — C03CA01.

ATC Vet — QC03CA01.

UNII — 7LXUSN7Z05.



NOTE. Compounded preparations of furosemide may be represented by the following names:

- Co-amlofruse (BAN)—furosemide 8 parts and amloride hydrochloride 1 part (w/w).

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

Ph. Eur. 6.8 (Furosemide). A white or almost white, crystalline powder. Practically insoluble in water and in dichloromethane; sparingly soluble in alcohol; soluble in acetone. It dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 33 (Furosemide). A white to slightly yellow, odourless, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone, in dimethylformamide, and in solutions of alkali hydroxides; very slightly soluble in chloroform; slightly soluble in ether; soluble in methyl alcohol. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Solutions for injection are prepared with the aid of sodium hydroxide, giving solutions with a pH of 8.0 to 9.3.

Incompatibility. Solutions of furosemide for injection are alkaline and should not be mixed or diluted with glucose injection or other acidic solutions.

Furosemide injection has been reported¹ to be visually incompatible with injections of diltiazem hydrochloride, dobutamine hydrochloride, dopamine hydrochloride, labetalol hydrochloride, midazolam hydrochloride, milrinone lactate, nicardipine hydrochloride, and vecuronium bromide. Incompatibility has also been noted with parenteral nutrient solutions,² with cisatracurium besylate,³ with levofloxacin,⁴ with phenylephrine,⁵ and with vasopressin.⁶

1. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; 54: 64-5.
2. Trissel LA, *et al.* Compatibility of parenteral nutrient solutions with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; 54: 1295-1300.
3. Trissel LA, *et al.* Compatibility of cisatracurium besylate with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; 54: 1735-41.
4. Saltsman CL, *et al.* Compatibility of levofloxacin with 34 medications during simulated Y-site administration. *Am J Health-Syst Pharm* 1999; 56: 1458-9.
5. Faria CE, *et al.* Visual compatibility of furosemide with phenylephrine and vasopressin. *Am J Health-Syst Pharm* 2006; 63: 906-8.

Stability. A study¹ showed that furosemide injection (10 mg/mL) in 25% human albumin solution was stable for 48 hours at room temperature when protected from light, and for 14 days under refrigeration. No bacterial or fungal growth was found.

1. Elwell RJ, *et al.* Stability of furosemide in human albumin solution. *Ann Pharmacother* 2002; 36: 423-6.

Adverse Effects

Most adverse effects of furosemide occur with high doses, and serious effects are uncommon. The most common adverse effect is fluid and electrolyte imbalance including hyponatraemia, hypokalaemia, and hypochloralcalcaemia, particularly after large doses or prolonged use. Signs of electrolyte imbalance include headache, hypotension, muscle cramps, dry mouth, thirst, weakness, lethargy, drowsiness, restlessness, oliguria, cardiac arrhythmias, and gastrointestinal disturbances. Hypovolaemia and dehydration may occur, especially in the elderly. The risk of hypokalaemia may be less with loop diuretics such as furosemide, which have a short duration of action, than with

The symbol † denotes a preparation no longer actively marketed

The symbol ⊗ denotes a substance whose use may be restricted in certain sports (see p.vii)

thiazide diuretics. Unlike the thiazides, furosemide increases the urinary excretion of calcium and nephrocalcinosis has been reported in preterm infants.

Furosemide may cause hyperuricaemia and precipitate gout in some patients. It may provoke hyperglycaemia and glycosuria, but probably to a lesser extent than the thiazide diuretics.

Pancreatitis and cholestatic jaundice seem to occur more often than with the thiazides. Other adverse effects include blurred vision, yellow vision, dizziness, headache, and orthostatic hypotension. Other adverse effects occur rarely. Rashes and photosensitivity reactions may be severe; hypersensitivity reactions include interstitial nephritis and vasculitis; fever has also been reported. Bone marrow depression may occur; there have been reports of agranulocytosis, thrombocytopenia, and leucopenia. Tinnitus and deafness may occur, in particular during rapid high-dose parenteral furosemide. Deafness may be permanent, especially in patients taking other ototoxic drugs.

Incidence of adverse effects. In a survey of 553 hospital inpatients¹ receiving furosemide 220 patients (40%) had 480 adverse reactions. Electrolyte disturbances occurred in 130 (23.5%) patients and extracellular volume depletion in 50 (9%). Adverse reactions were more common in those with liver disease, and hepatic coma occurred in 20 patients with hepatic cirrhosis. A similar survey in 585 hospital inpatients² revealed 177 adverse effects in 123 (21%). These included volume depletion in 85 patients (14.5%), hypokalaemia in 21 (3.6%), and hyponatraemia in 6 (1%). Hypokalaemia was considered to be life-threatening in 2 patients. Hyperuricaemia occurred in 54 patients (9.2%), of whom 40 also had volume depletion, and clinical gout developed in 2.

1. Naranjo CA, et al. Furosemide-induced adverse reactions during hospitalization. *Am J Hosp Pharm* 1978; **35**: 794-8.
2. Lowe J, et al. Adverse reactions to furosemide in hospital inpatients. *BMJ* 1979; **2**: 360-2.

Carcinogenicity. See under Hydrochlorothiazide, p.1438.

Dementia. Licensed product information states that more deaths were seen in elderly patients with dementia who were taking risperidone and furosemide than in those taking either drug alone; use of risperidone with other diuretics (mainly low-dose thiazides) was not associated with such findings. See also under Risperidone, p.1131.

Effects on bone. The hypercalcaemia caused by loop diuretics may alter bone metabolism, but the clinical significance of this is unknown. Results of studies have been conflicting: some have failed to show an adverse effect on bone mineral density¹ or risk of fracture² with loop diuretics, while others have reported a greater degree of bone loss³ and an increased risk of fractures^{4,5} in both men and women taking loop diuretics. However, the magnitude of effect has, at best, been modest, and interpretation of results has been complicated by confounding factors.

For mention of effects on bone in children (possibly associated with secondary hyperparathyroidism) see Effects in Infants and Neonates, below.

1. Lim LS, et al. Diuretic use and bone mineral density in older USA men: the osteoporotic fractures in men (MrOS) study. *Age Ageing* 2005; **34**: 504-7.
2. Lim LS, et al. Loop diuretic use and rates of hip bone loss and risk of falls and fractures in older women. *J Am Geriatr Soc* 2009; **57**: 855-62.
3. Lim LS, et al. Osteoporotic Fractures in Men (MrOS) Study Group. Loop diuretic use and increased rates of hip bone loss in older men: the Osteoporotic Fractures in Men Study. *Arch Intern Med* 2008; **168**: 735-40.
4. Rejnmark L, et al. Fracture risk in patients treated with loop diuretics. *J Intern Med* 2006; **259**: 117-24.
5. Carbone LD, et al. Loop diuretic use and fracture in postmenopausal women: findings from the Women's Health Initiative. *Arch Intern Med* 2009; **169**: 132-40.

Effects on the ears. Ototoxicity and deafness during furosemide therapy is most frequently associated with elevated blood concentrations resulting from rapid intravenous infusion¹ or delayed excretion in patients with renal impairment.² Of 29 cases of furosemide-induced deafness reported to the FDA³ in the USA, most patients had renal disease or had received the drug intravenously. Eight patients had also received another ototoxic drug. However, deafness occurred in 11 patients after oral use, and in 4 of these hearing loss occurred in the absence of renal disease or other ototoxic drugs. Hearing loss was generally transient, lasting from one-half to 24 hours, but permanent hearing loss occurred in 3 patients, one of whom had taken furosemide orally. Deafness was not always associated with high doses; six patients had received a total of 200 mg or less of furosemide. See also Precautions, below.

1. Heidland A, Wigand ME. Einfluss hoher Furosemiddosen auf die Gehörfunktion bei Uramie. *Klin Wochenschr* 1970; **48**: 1052-6.

2. Schwartz GH, et al. Ototoxicity induced by furosemide. *N Engl J Med* 1970; **282**: 1413-14.
3. Gallagher KL, Jones JK. Furosemide-induced ototoxicity. *Ann Intern Med* 1979; **91**: 744-5.

Effects on electrolyte balance. CALCIUM. Furosemide increases renal calcium excretion. There is a danger of hypocalcaemic tetany during furosemide use in hypoparathyroid patients¹ and it has also been reported² in a patient with latent hypoparathyroidism following thyroidectomy.

The decrease in serum-calcium concentrations could also induce hyperparathyroidism. In a study involving 36 patients with heart failure, furosemide was associated with elevations in both parathyroid hormone and alkaline phosphatase concentrations, possibly indicating accelerated bone remodelling such as that found in primary hyperparathyroidism.³

For the suggestion that hypercalcaemia in those taking loop diuretics may affect bone metabolism, see Effects on Bone, above. For reports of hypercalcaemia, rickets, renal calculi, and hyperparathyroidism in neonates given furosemide, see Effects in Infants and Neonates, below.

1. Gabow PA, et al. Furosemide-induced reduction in ionized calcium in hypoparathyroid patients. *Ann Intern Med* 1977; **86**: 579-81.
2. Bashey A, MacNee W. Tetany induced by furosemide in latent hypoparathyroidism. *BMJ* 1987; **295**: 960-1.
3. Elmgren J, et al. Elevated serum parathyroid hormone concentration during treatment with high ceiling diuretics. *Eur J Clin Pharmacol* 1980; **18**: 363-4.

MAGNESIUM, POTASSIUM, AND SODIUM. For discussions of the effects of diuretics on these electrolytes see under the Adverse Effects of Hydrochlorothiazide, p.1438.

Effects in infants and neonates. Furosemide is commonly used in the treatment of cardiac and pulmonary disorders in premature infants and neonates. This age group appears to be particularly susceptible to adverse effects arising from the increase in urinary calcium excretion which occurs during long-term use. Increases in parathyroid hormone concentration^{1,2} and evidence of bone resorption^{1,3} support the suggestion that the increased calcium loss causes secondary hyperparathyroidism. There have been reports of decreased mineral content of bone,^{1,3} rickets,⁴ fractures,³ and renal calcification.^{1,5-7} An observation⁸ that renal calcification could be reversed by the addition of a thiazide diuretic was supported by other workers.⁶ There is evidence⁸ that furosemide-related renal calcifications in very low birth-weight infants might be associated with long-term renal impairment. Renal calcification has also been reported after furosemide use in older infants.⁹

It has been suggested¹⁰ that a sodium deficit in infants given furosemide for heart failure may contribute to a failure to thrive.

Concern has been expressed over the finding¹¹ that furosemide use in premature infants with respiratory distress syndrome increases the incidence of patent ductus arteriosus. The mechanism is thought to be connected with stimulation of renal prostaglandin- E_2 . However, the increased incidence of patent ductus arteriosus did not adversely affect the mortality in infants given furosemide, and a subsequent study¹² failed to find any increase in the incidence of patent ductus arteriosus in infants treated with furosemide compared with a control group. Paradoxically, furosemide has been used in the management of delayed closure of ductus (see Patent Ductus Arteriosus under Uses and Administration, below). There is a possibility that furosemide may not be effective in infants given indomethacin¹³ but it can prevent the decline in urine output that occurs during indomethacin use.^{14,15}

1. Venkataraman PS, et al. Secondary hyperparathyroidism and bone disease in infants receiving long-term furosemide therapy. *Am J Dis Child* 1983; **137**: 1157-61.
2. Vileisis RA. Furosemide effect on mineral status of parenterally nourished premature neonates with chronic lung disease. *Pediatrics* 1990; **85**: 316-22.
3. Morgan ME, Evans SE. Osteopenia in very low birthweight infants. *Lancet* 1986; **ii**: 1399-1400.
4. Chudley AE, et al. Nutritional rickets in 2 very low birthweight infants with chronic lung disease. *Arch Dis Child* 1980; **55**: 687-90.
5. Hufnagle KG, et al. Renal calcifications: a complication of long-term furosemide therapy in preterm infants. *Pediatrics* 1982; **70**: 360-3.
6. Noe HN, et al. Urolithiasis in pre-term neonates associated with furosemide therapy. *J Urol (Baltimore)* 1984; **132**: 93-4.
7. Pearce DM, et al. Sonographic diagnosis of furosemide-induced nephrocalcinosis in newborn infants. *J Ultrasound Med* 1984; **3**: 553-6.
8. Downing GJ, et al. Kidney function in very low birth weight infants with furosemide-related renal calcifications at ages 1 to 2 years. *J Pediatr* 1992; **120**: 599-604.
9. Alon US, et al. Nephrocalcinosis and nephrolithiasis in infants with congestive heart failure treated with furosemide. *J Pediatr* 1994; **125**: 149-51.
10. Salmon AP, et al. Sodium balance in infants with severe congestive heart failure. *Lancet* 1989; **ii**: 875.
11. Green TP, et al. Furosemide promotes patent ductus arteriosus in premature infants with respiratory-distress syndrome. *N Engl J Med* 1983; **308**: 743-8.
12. Yeh TF, et al. Early furosemide therapy in premature infants (≤ 2000 gm) with respiratory distress syndrome: a randomized controlled trial. *J Pediatr* 1984; **105**: 603-9.
13. Friedman Z, et al. Urinary excretion of prostaglandin E following the administration of furosemide and indomethacin to sick low-birth-weight infants. *J Pediatr* 1978; **93**: 512-15.

14. Yeh TF, et al. Furosemide prevents the renal side effects of indomethacin therapy in premature infants with patent ductus arteriosus. *J Pediatr* 1982; **101**: 433-7.
15. Nahata MC, et al. Furosemide can prevent decline in urine output in infants receiving indomethacin for patent ductus closure: a multidose study. *Infusion* 1988; **12**: 11-12 and 15.

Effects on lipid metabolism. Most studies into the effects of diuretics on blood-lipid concentrations have used thiazides (see Hydrochlorothiazide, p.1439). The few studies into the effects of furosemide suggest that, like thiazides, it may adversely influence blood-lipid concentrations during short-term use.¹

1. Ames RP. The effects of antihypertensive drugs on serum lipids and lipoproteins I: diuretics. *Drugs* 1986; **32**: 260-78.

Precautions

Precautions and contra-indications for furosemide that are dependent on its effects on fluid and electrolyte balance are similar to those of the thiazide diuretics (see Hydrochlorothiazide, p.1440). Although furosemide is used in high doses for oliguria due to chronic or acute renal impairment it should not be given in anuria or in renal failure caused by nephrotoxic or hepatotoxic drugs nor in renal failure associated with hepatic coma. Furosemide should not be given in pre-comatose states associated with hepatic cirrhosis. It should be used with care in patients with prostatic hyperplasia or impairment of micturition since it can precipitate acute urinary retention.

To reduce the risk of ototoxicity, licensed product information recommends that furosemide should not be injected intravenously at a rate exceeding 4 mg/minute although the *BNF 59* advises that a single dose of up to 80 mg may be given more rapidly.

Furosemide should be used with caution during pregnancy and breast feeding since it crosses the placenta and also appears in breast milk. Furosemide may compromise placental perfusion by reducing maternal blood volume; it may also inhibit lactation.

Hepatic impairment. In patients with chronic heart failure and moderate liver congestion, high-dose furosemide therapy could produce increases in liver enzymes suggestive of hepatitis.¹ Special care should be taken in such patients to avoid severe ischaemic liver damage caused by a drop in systemic blood pressure.

As with the thiazides, furosemide should be avoided in patients with severe hepatic impairment.

1. Lang I, et al. Furosemide and increases in liver enzymes. *Ann Intern Med* 1988; **109**: 845.

Hypersensitivity. Furosemide is a sulfur-containing diuretic and hypersensitivity reactions may occur, although they are rare; cross-reactivity with other sulfur-containing drugs is also possible. However, 2 patients who had in the distant past shown serious adverse reactions to sulfur-containing diuretics were successfully treated¹ with furosemide using a rechallenge protocol. They were given an initial dose of 50 micrograms which was increased gradually each day to 20 mg by day 10, and were discharged from hospital on a maintenance dose of 40 mg twice daily. Another patient² with a history of sulfonamide-induced pancreatitis developed pancreatitis with furosemide, which recurred with bumetanide and torsemide and on rechallenge with furosemide. She underwent a rapid desensitisation regimen and was subsequently successfully stabilised on oral furosemide. Others have also described rapid desensitisation protocols.³

1. Earl G, et al. Furosemide challenge in patients with heart failure and adverse reactions to sulfa-containing diuretics. *Ann Intern Med* 2003; **138**: 358-9.
2. Juang P, et al. Probable loop diuretic-induced pancreatitis in a sulfonamide-allergic patient. *Ann Pharmacother* 2006; **40**: 128-34.
3. Alim N, Patel JY. Rapid oral desensitization to furosemide. *Ann Allergy Asthma Immunol* 2009; **103**: 538.

Hypoparathyroidism. For comments on the possibility of hypocalcaemic tetany in hypoparathyroid patients taking furosemide, see Effects on Electrolyte Balance, above.

Infants and neonates. Caution must be exercised in using furosemide in infants, particularly for long periods. The immaturity of the renal system can result in unexpectedly high blood concentrations and extended half-lives. **Fluid and electrolyte balances** should therefore be monitored carefully. Neonates appear to be particularly susceptible to increases in urinary calcium concentrations after long-term use. There have also been reports¹ of an increased incidence of patent ductus arteriosus in infants given furosemide, although this did not adversely affect mortality.

Secondly, several studies²⁻⁴ have shown furosemide to be a potent displacer of **bilirubin** from albumin binding sites and it should be used with caution in jaundiced infants. On a molar basis chlorothiazide, furosemide, and etacrynic acid were at least as potent as sulfafurazole in displacing bilirubin from albumin.⁵ Doses of furosemide 1 mg/kg probably do not produce a significant

cant increase in free bilirubin in most jaundiced infants,^{3,4} although doses greater than 1.5 mg/kg or repeated dosing could potentially do so.⁴ Chlorothiazide 15 to 20 mg/kg would not be an appropriate alternative to furosemide² since it could produce higher plasma bilirubin concentrations in jaundiced infants.

In addition, there is some evidence from an *in vitro* study⁵ that bilirubin may displace furosemide from binding sites to a greater extent in neonates than in adults. The clearance of furosemide is much slower in neonates than in adults, with an eightfold prolongation in plasma half-life, and this should be taken into account during repeat dosing.⁴

1. Green TP, et al. Furosemide promotes patent ductus arteriosus in premature infants with the respiratory-distress syndrome. *N Engl J Med* 1983; 308: 743-8.
2. Shankaran S, Poland RL. The displacement of bilirubin from albumin by furosemide. *J Pediatr* 1977; 90: 642-6.
3. Wennberg RP, et al. Displacement of bilirubin from human albumin by three diuretics. *J Pediatr* 1977; 90: 647-50.
4. Aranda JV, et al. Pharmacokinetic disposition and protein binding of furosemide in newborn infants. *J Pediatr* 1978; 93: 507-11.
5. Viani A, Pacifici GM. Bilirubin displaces furosemide from serum protein: the effect is greater in newborn infants than adult subjects. *Dev Pharmacol Ther* 1990; 14: 90-5.

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

Interactions

The interactions of furosemide that are due to its effects on fluid, electrolyte, and carbohydrate balance are similar to those of hydrochlorothiazide (see p.1440).

Furosemide may enhance the nephrotoxicity of cephalosporin antibacterials such as cefalotin and can enhance the ototoxicity of aminoglycoside antibacterials and other ototoxic drugs.

Aliskiren. Licensed product information for aliskiren states that it may significantly decrease furosemide concentrations.

Antiepileptics. The diuretic effect of furosemide has been shown to be substantially reduced by mixed antiepileptic therapy that included phenytoin.^{1,2} The mean diuretic effect of furosemide 20 mg or 40 mg orally in patients on such therapy was 68% and 51% that of healthy controls respectively.¹

For the effect of furosemide on *phenobarbital*, see p.538.

Symptomatic hyponatraemia has been associated with the use of furosemide or hydrochlorothiazide with carbamazepine.³

1. Ahmad S. Renal insensitivity to furosemide caused by chronic anticonvulsant therapy. *BMJ* 1974; 3: 657-9.
2. Fine A, et al. Malabsorption of furosemide caused by phenytoin. *BMJ* 1977; 2: 1061-2.
3. Yassa R, et al. Carbamazepine, diuretics, and hyponatraemia: a possible interaction. *J Clin Psychiatry* 1987; 48: 281-3.

Diuretics. Severe electrolyte disturbances may occur in patients given metolazone with furosemide.

Hypnotics. A syndrome of flushing, tachycardia, elevated blood pressure, and severe diaphoresis was reported after intravenous dosage of furosemide in 6 patients who had taken cloral hydrate orally during the preceding 24 hours.¹ The reaction occurred in 1 patient on a subsequent occasion when given both drugs but not when furosemide was used without cloral hydrate. A subsequent retrospective study² among 43 patients who had received both cloral hydrate and furosemide showed that 1 patient had suffered a similar reaction; of 2 further patients who had possibly been affected, 1 had subsequently taken both drugs without adverse effects. A similar interaction has been reported in an 8-year-old child.³

1. Malach M, Berman N. Furosemide and cloral hydrate: adverse drug interaction. *JAMA* 1975; 232: 638-9.
2. Pevonka MP, et al. Interaction of cloral hydrate and furosemide: a controlled retrospective study. *Drug Intell Clin Pharm* 1977; 11: 332-5.
3. Dean RP, et al. Interaction of cloral hydrate and intravenous furosemide in a child. *Clin Pharm* 1991; 10: 385-7.

Lithium. For reports of a possible increase in plasma-lithium concentrations in patients receiving loop diuretics, see p.436.

NSAIDs. NSAIDs may antagonise the diuretic effect of furosemide and other diuretics.¹ Use of NSAIDs with diuretics may increase the risk of nephrotoxicity, although it has also been suggested that furosemide may protect against the renal effects of indometacin in infants (see Effects in Infants and Neonates, above).

1. Webster J. Interactions of NSAIDs with diuretics and β -blockers: mechanisms and clinical implications. *Drugs* 1985; 30: 32-41.

Probenecid. Probenecid has been shown¹⁻⁴ to reduce the renal clearance of furosemide, and to reduce the diuretic effect.^{2,3}

1. Honari J, et al. Effects of probenecid on furosemide kinetics and natriuresis in man. *Clin Pharmacol Ther* 1977; 22: 395-401.
2. Odland B, Beermann B. Renal tubular secretion and effects of furosemide. *Clin Pharmacol Ther* 1980; 27: 784-90.
3. Smith DE, et al. Preliminary evaluation of furosemide-probenecid interaction in humans. *J Pharm Sci* 1980; 69: 571-5.
4. Vree TB, et al. Probenecid inhibits the renal clearance of furosemide and its acyl glucuronide. *Br J Clin Pharmacol* 1995; 39: 692-5.

Tobacco. The effects of tobacco smoking on the pharmacokinetics of furosemide have been reviewed.^{1,2} Nicotine inhibits diuresis and diminishes the diuretic effect of furosemide. However, this effect is attenuated in habitual smokers.

1. Miller LG. Recent developments in the study of the effects of cigarette smoking on clinical pharmacokinetics and clinical pharmacodynamics. *Clin Pharmacokinet* 1989; 17: 90-108.
2. Miller LG. Cigarettes and drug therapy: pharmacokinetic and pharmacodynamic considerations. *Clin Pharm* 1990; 9: 125-35.

Xanthines. For the effect of furosemide on *theophylline*, see Diuretics, p.1260.

Pharmacokinetics

Furosemide is fairly rapidly absorbed from the gastrointestinal tract; bioavailability has been reported to be about 60 to 70% but absorption is variable and erratic. The half-life of furosemide is up to about 2 hours although it is prolonged in neonates and in patients with renal and hepatic impairment. Furosemide is up to 99% bound to plasma albumin, and is mainly excreted in the urine, largely unchanged. There is also some excretion via the bile and non-renal elimination is considerably increased in renal impairment. Furosemide crosses the placental barrier and is distributed into breast milk. The clearance of furosemide is not increased by haemodialysis.

◊ The pharmacokinetics of furosemide have been extensively reviewed.¹⁻⁶ The development of an analytical method using HPLC with fluorescence has produced greater sensitivity and more consistent results. Absorption after oral use is erratic and is subject to large inter- and intra-individual variation. It is influenced by the dosage form, underlying disease processes, and by the presence of food. Furosemide absorption in patients with heart failure has been reported to be even more erratic than in healthy subjects. The bioavailability of furosemide from oral dosage forms is also highly variable with reported values ranging from 20 to 100%. It is influenced by factors affecting absorption but the poor solubility of furosemide does not appear to have a major influence on bioavailability and *in vitro* dissolution data may not reflect *in vivo* bioavailability. Bioavailability tends to be decreased by about 10% in patients with renal disease, and slightly increased in liver disease. Values are erratic in patients with heart disease.

Furosemide is highly bound to plasma proteins, almost exclusively to albumin. The proportion of free (unbound) furosemide is higher in patients with heart disease, renal impairment, and cirrhosis of the liver. Patients with liver disease also have an increased apparent volume of distribution which is proportionally greater than the decrease seen in protein binding. Patients with nephrotic syndrome have significant proteinuria and secondary hypoalbuminaemia. This results in reduced protein binding in the blood, particularly at higher blood concentrations, and binding to proteins present in the urine, which may account for the resistance to furosemide therapy reported in these patients.

A glucuronide metabolite of furosemide is produced in varying amounts. The site of metabolism is unknown at present. There is debate over another potential metabolite, 4-chloro-5-sulfamoyl anthranilic acid (CSA). It has been argued³ that it is an artefact produced during the extraction procedures although there is some evidence to refute this.⁴

A half-life for furosemide in healthy subjects has generally been reported in the range of 30 to 120 minutes. In patients with end-stage renal disease the average half-life is 9.7 hours. The half-life may be slightly longer in patients with hepatic dysfunction and a range of 50 to 327 minutes has been reported in patients with heart failure. In severe multi-organ failure the half-life may range from 20 to 24 hours.

Furosemide clearance is influenced by age, underlying disease state, and drug interactions. Clearance reduces with increasing age, probably due to declining renal function. Renal impairment in renal or cardiac disease reduces renal clearance, although this may be compensated for by increases in non-renal clearance. Hepatic impairment has little impact on clearance. Renal and non-renal clearance may be reduced by probenecid and indometacin. The efficacy of furosemide as a diuretic depends upon it reaching its site of action, the renal tubules, unchanged. About one-half to two-thirds of an intravenous dose or one-quarter to one-third of an oral dose are excreted unchanged, the difference being largely due to the poor bioavailability from the oral route. The effect of furosemide is more closely related to its urinary excretion than to the plasma concentration. Urinary excretion may be reduced in renal impairment due to reduced renal blood flow and reduced tubular secretion.

1. Cutler RE, Blair AD. Clinical pharmacokinetics of furosemide. *Clin Pharmacokinet* 1979; 4: 279-96.
2. Benet LZ. Pharmacokinetics/pharmacodynamics of furosemide in man: a review. *J Pharmacokinet Biopharm* 1979; 7: 1-27.
3. Hammarlund-Udenaes M, Benet LZ. Furosemide pharmacokinetics and pharmacodynamics in health and disease—an update. *J Pharmacokinet Biopharm* 1989; 17: 1-46.
4. Ponto LLB, Schoenwald RD. Furosemide (frusemide): a pharmacokinetic/pharmacodynamic review (part I). *Clin Pharmacokinet* 1990; 18: 381-408.

5. Ponto LLB, Schoenwald RD. Furosemide (frusemide): a pharmacokinetic/pharmacodynamic review (part II). *Clin Pharmacokinet* 1990; 18: 460-71.

6. Vrhovac B, et al. Pharmacokinetic changes in patients with oedema. *Clin Pharmacokinet* 1995; 28: 405-18.

Infants and neonates. The half-life of furosemide in term and preterm neonates is markedly prolonged compared with that in adults.^{1,2} Half-lives of 4.5 to 46 hours have been reported and it has been suggested that the prolongation may be greater in preterm than in term neonates. This effect is due mainly to immature renal function and if repeated doses are necessary over a short period accumulation may occur.¹

1. Besunder JB, et al. Principles of drug biotransformation in the neonate: a critical evaluation of the pharmacokinetic-pharmacodynamic interface (part II). *Clin Pharmacokinet* 1988; 14: 261-86.

2. Aranda JV, et al. Pharmacokinetic disposition and protein binding of furosemide in newborn infants. *J Pediatr* 1978; 93: 507-11.

Uses and Administration

Furosemide is a potent diuretic with a rapid action. Like the other loop or high-ceiling diuretics it is used in the treatment of oedema associated with heart failure (below), including pulmonary oedema, and with renal and hepatic disorders (but see Precautions, above) and may be effective in patients unresponsive to thiazide diuretics. It is also used in high doses in the management of oliguria due to renal failure or insufficiency. Furosemide is also used in the treatment of hypertension (p.1290), either alone or with other antihypertensives.

Furosemide inhibits the reabsorption of electrolytes mainly in the thick ascending limb of the loop of Henle and also in the distal renal tubules. It may also have a direct effect in the proximal tubules. Excretion of sodium, potassium, calcium, and chloride ions is increased and water excretion enhanced. It has no clinically significant effect on carbonic anhydrase. See Action, below, for further reference to its mechanism of action.

Administration and dosage. Furosemide's effects are evident within 30 minutes to 1 hour after an oral dose, peak at 1 to 2 hours, and last for about 4 to 6 hours; after intravenous injection its effects are evident in about 5 minutes and last for about 2 hours. It is given orally, usually in the morning. Alternatively it may be given intramuscularly or intravenously as the sodium salt; doses are expressed in terms of furosemide base. 10.7 mg of furosemide sodium is equivalent to about 10 mg of furosemide base. Licensed product information recommends that whether by direct intravenous injection or by infusion the rate of intravenous dosage should not exceed 4 mg/minute although the *BNF* 59 advises that a single dose of up to 80 mg may be given more rapidly.

Unlike the thiazide diuretics where, owing to their flat dose-response curve, very little is gained by increasing the dose, furosemide has a steep dose-response curve, which gives it a wide therapeutic range.

In the treatment of **oedema**, the usual initial oral dose is 40 mg once daily, adjusted as necessary according to response. Mild cases may respond to 20 mg daily or 40 mg on alternate days. Some patients may need doses of 80 mg or more daily given as one or two doses daily, or intermittently. Severe cases may require gradual titration of the furosemide dosage up to 600 mg daily. In an emergency or when oral therapy cannot be given, 20 to 50 mg of furosemide may be given by slow intravenous injection; intramuscular injection may be given in exceptional cases but is not suitable for acute conditions. If necessary further doses may be given, increasing by 20-mg increments and not given more often than every 2 hours. If doses above 50 mg are required they should be given by slow intravenous infusion. For pulmonary oedema, if an initial slow intravenous injection of 40 mg does not produce a satisfactory response within one hour, a further 80 mg may be given slowly intravenously.

In the treatment of **hypertension**, furosemide is given in oral doses of 40 to 80 mg daily, either alone, or with other antihypertensives.

High-dose therapy. In the management of **oliguria** in acute or chronic renal failure where the glomerular filtration rate is less than 20 mL/minute but greater than 5 mL/minute, furosemide 250 mg diluted to 250 mL in a suitable diluent is infused over one hour. If urine output is insufficient within the next hour, this dose may be followed by 500 mg added to an appropriate infusion fluid, the total volume of which must be governed by the patient's state of hydration, and infused over about 2 hours. If a satisfactory urine output has still not been achieved within one hour of the end of the second infusion then a third dose of 1 g may be infused over about 4 hours. The rate of infusion should never exceed 4 mg/minute. In oliguric patients with significant fluid overload, the injection may be given without dilution directly into the vein, using a constant rate infusion pump with a micrometer screw-gauge adjustment; the rate should still never exceed 4 mg/minute. Patients who do not respond to a dose of 1 g probably require dialysis. If the response to either dosage method is satisfactory, the effective dose (of up to 1 g) may then be repeated every 24 hours. Dosage adjustments should subsequently be made according to the patient's response. Alternatively, oral treatment may be maintained; 500 mg should be given orally for each 250 mg required by injection.

When used in chronic renal impairment, an initial oral dose of 250 mg may be given, increased, if necessary in steps of 250 mg every 4 to 6 hours to a maximum of 1.5 g in 24 hours; in exceptional cases up to 2 g in 24 hours may be given. Dosage adjustments should subsequently be made according to the patient's response.

During treatment with these high-dose forms of furosemide therapy, careful laboratory control is essential. Fluid balance and electrolytes should be carefully controlled and, in particular, in patients with shock, measures should be taken to correct the blood pressure and circulating blood volume, before starting this type of treatment. High-dose furosemide therapy is contra-indicated in renal failure caused by nephrotoxic or hepatotoxic drugs, and in renal failure associated with hepatic coma.

For doses in children, see below.

Action. The mechanism of action of furosemide is not fully understood.¹ It appears to act mainly by inhibiting active reabsorption of chloride ions in the ascending limb of the loop of Henle. Urinary excretion of sodium, chloride, potassium, hydrogen, calcium, magnesium, ammonium, bicarbonate, and possibly phosphate is increased; the chloride excretion exceeds that of sodium and there is an enhanced exchange of sodium for potassium leading to greater excretion of potassium. The resulting low osmolality of the medulla inhibits the reabsorption of water by the kidney. There is a possibility that furosemide may also act at a more proximal site.

In addition to its diuretic actions, furosemide has been shown to increase peripheral venous capacitance and reduce forearm blood flow. It also reduces renal vascular resistance with a resultant increase in renal blood flow the degree of which is proportional to the initial resistance.

Furosemide has been shown to increase plasma-renin activity, plasma-noradrenaline concentrations, and plasma-angiotensin-converting enzyme concentrations. Alterations in the renin-angiotensin-aldosterone system may play a part in the development of acute tolerance. Furosemide increases renal-prostaglandin concentrations but it is unknown whether this is due to increased synthesis or inhibition of degradation or both. Prostaglandins appear to mediate the diuretic/natriuretic action. The primary effects appear to be alterations in renal haemodynamics with subsequent increases in electrolyte and fluid excretion.

The diuretic response to furosemide is related to the concentration in the urine, not to that in the plasma. Furosemide is delivered to the renal tubules by a non-specific organic acid pump in the proximal tubules.¹

In some cases sodium intake may be sufficient to overcome the diuretic effect, and limiting sodium intake could restore responsiveness.²

1. Ponto LLB, Schaenwald RD. Furosemide (frusemide): a pharmacokinetic/pharmacodynamic review (part I). *Clin Pharmacokinet* 1990; 18: 381-408.

2. Brater DC. Resistance to loop diuretics: why it happens and what to do about it. *Drugs* 1985; 30: 427-43.

Administration. Continuous intravenous infusion of loop diuretics may be more effective than intermittent intravenous bolus

injection and may provide a more consistent urine flow with fewer alterations in urine balance.^{1,2} Bumetanide was more effective by continuous infusion than as bolus doses in 8 patients with severe chronic renal impairment.³ In 20 patients with chronic heart failure requiring high-dose furosemide therapy, furosemide given by continuous infusion was more effective than the same dose by bolus injection.⁴ The lower plasma concentrations associated with continuous infusion may also reduce the risk of toxicity.

1. Yelton SL, et al. The role of continuous infusion loop diuretics. *Ann Pharmacother* 1995; 29: 1010-14.

2. Gulbis BE, Spencer AP. Efficacy and safety of a furosemide continuous infusion following cardiac surgery. *Ann Pharmacother* 2006; 40: 1797-1803.

3. Rudy DW, et al. Loop diuretics for chronic renal insufficiency: a continuous infusion is more efficacious than bolus therapy. *Ann Intern Med* 1991; 115: 360-6.

4. Dormans TPJ, et al. Diuretic efficacy of high dose furosemide in severe heart failure: bolus injection versus continuous infusion. *J Am Coll Cardiol* 1996; 28: 376-82.

Administration in children. Furosemide has been given to neonates, infants, and children in the treatment of oedema and oliguria. For **oedema**, UK licensed product information allows an oral dose of 1 to 3 mg/kg daily in the morning, to a maximum of 40 mg daily, or an intravenous injection or infusion of 0.5 to 1.5 mg/kg daily, to a maximum of 20 mg daily. Alternatively, the *BNFC* 2009 suggests the following regimens, given according to age:

Oral

- neonate: 0.5 to 2 mg/kg every 12 to 24 hours (every 24 hours if postmenstrual age is under 31 weeks)
- 1 month to 12 years: 0.5 to 2 mg/kg given 2 to 3 times daily (every 24 hours if postmenstrual age is under 31 weeks); higher doses may be required in resistant oedema. Maximum daily dose is the smaller of 12 mg/kg or 80 mg
- 12 years and above: usually 20 to 40 mg daily; 80 to 120 mg permitted in resistant oedema

Slow intravenous injection

- neonate: 0.5 to 1 mg/kg every 12 to 24 hours (every 24 hours if postmenstrual age under 31 weeks)
- 1 month to 12 years: 0.5 to 1 mg/kg (maximum 4 mg/kg) every 8 hours as necessary
- 12 years and above: 20 to 40 mg every 8 hours as necessary. Resistant oedema may require higher doses

Continuous intravenous infusion

- 1 month to 18 years: 0.1 to 2 mg/kg per hour. After cardiac surgery, the lower dose of 100 micrograms/kg per hour should be given initially, and doubled every 2 hours until urine output exceeds 1 mL/kg per hour

In the treatment of **oliguria**, the *BNFC* 2009 suggests the following doses:

Oral

- 12 to 18 years: an initial dose of 250 mg daily, adjusted if necessary by 250 mg increments given every 4 to 6 hours. A maximum single dose of 2 g is permitted, but rarely used.

Intravenous infusion

- 1 month to 12 years: 2 to 5 mg/kg up to 4 times daily (maximum 1 g daily)
- 12 to 18 years: an initial dose of 250 mg given over 1 hour at a rate not exceeding 4 mg/minute. If a satisfactory urine output is not obtained, a further 500 mg may be given over 2 hours, then a further 1 g over 4 hours. If no response is obtained, dialysis is probably required. The effective dose (up to 1 g) may be repeated every 24 hours.

Ascites. Dietary sodium restriction and diuretics are mainstays of the management of cirrhotic ascites (p.1276). Spironolactone is usually the diuretic of first choice, but furosemide may be added to therapy as necessary.

Bronchopulmonary dysplasia. Bronchopulmonary dysplasia is a major cause of chronic lung disease in infants. Treatment often involves the use of corticosteroids (see p.1638). Additional supportive therapy may include the use of diuretics such as furosemide.

Alternate-day therapy with oral furosemide 4 mg/kg has produced modest benefits in pulmonary status in the absence of a diuretic effect, and few adverse effects.¹ Improved pulmonary function has occurred in infants given furosemide 1 mg/kg parenterally after packed red blood cell transfusions, given to improve oxygen-carrying capacity.² The successful use of nebulised furosemide in a dose of 1 mg/kg has been reported;^{3,4} again pulmonary status was improved without production of diuresis or renal adverse effects. However, a single inhaled dose of 1 mg/kg failed to improve pulmonary mechanics in another study involving older infants with more severe disease.⁵ Systematic reviews of the use of intravenous or oral,⁶ or nebulised⁷ diuretics in preterm infants with chronic lung disease concluded that, although there were improvements in pulmonary function, there was insufficient evidence to recommend routine use.

1. Rush MG, et al. Double-blind, placebo-controlled trial of alternate-day furosemide therapy in infants with chronic bronchopulmonary dysplasia. *J Pediatr* 1990; 117: 112-18.

2. Stefano JL, Bhutani VK. Role of furosemide therapy after booster-packed erythrocyte transfusions in infants with bronchopulmonary dysplasia. *J Pediatr* 1990; 117: 965-8.

3. Rastogi A, et al. Nebulized furosemide in infants with bronchopulmonary dysplasia. *J Pediatr* 1994; 125: 976-9.

4. Prabhu VG, et al. Pulmonary function changes after nebulised and intravenous furosemide in ventilated premature infants. *Arch Dis Child* 1997; 77: F32-F35.

5. Kugelman A, et al. Pulmonary effect of inhaled furosemide in ventilated infants with severe bronchopulmonary dysplasia. *Pediatrics* 1997; 99: 71-5.

6. Brion LP, Primhak RA. Intravenous or enteral loop diuretics for preterm infants with (or developing) chronic lung disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 24/06/05).

7. Brion LP, et al. Aerosolized diuretics for preterm infants with (or developing) chronic lung disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 07/05/08).

Haemolytic-uraemic syndrome. Renal failure is a possible consequence of the haemolytic-uraemic syndrome (see Thrombotic Microangiopathies, p.1185). Correction of any hypovolaemic state with adequate fluids and of oliguria by inducing diuresis with furosemide may be used to prevent this.

Of 54 children with haemolytic-uraemic syndrome given intravenous furosemide 2.5 to 4 mg/kg every 3 to 4 hours immediately after diagnosis 24% eventually required dialysis.¹ In contrast, a retrospective analysis of 39 patients treated conservatively showed that 82% had required dialysis. The results therefore suggested that high-dose furosemide could prevent the progression of oliguria to anuria in these patients by increasing urine clearance.

1. Rousseau E, et al. Decreased necessity for dialysis with loop diuretic therapy in hemolytic uremic syndrome. *Clin Nephrol* 1990; 34: 22-5.

Heart failure. Diuretics have been the mainstay in the treatment of heart failure (p.1284) but drugs such as ACE inhibitors that have been shown to improve mortality are now generally recommended for first-line therapy along with diuretics. Diuretics provide very effective symptomatic control in patients with peripheral or pulmonary oedema and rapidly relieve dyspnoea. If symptoms of fluid retention are only mild, a thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide, may be adequate. However, in most cases, especially in moderate or severe fluid retention, a loop diuretic such as furosemide will be necessary. Combination treatment with diuretics that behave synergistically by acting at different sites (the principle of sequential nephron blockade), namely a loop diuretic with a thiazide or potassium-sparing diuretic, may be needed in some patients, especially when there is diuretic resistance.

Patients have been successfully treated using continuous intravenous infusions¹ or high doses (up to 8 g daily) of furosemide given by intravenous infusion^{2,3} or orally.⁴ A patient who was successfully maintained on intravenous furosemide at home has been described.⁵ Combination of furosemide with thiazide diuretics⁶ or metolazone^{6,7} has been reported. There is a danger of overdiuresis with both of these strategies, and careful monitoring of electrolytes and renal function is essential.⁸ Delivery of furosemide to the renal tubules may be enhanced by combined therapy with hydralazine⁹ or captopril.¹⁰ The use of captopril and furosemide may also correct hyponatraemia without fluid restriction.¹¹ In elderly patients not responding adequately to low-dose furosemide with optimum doses of ACE inhibitors, increasing the dose of furosemide (to an average of 297 mg daily orally) has been reported¹² to be of benefit. However, caution is necessary when using furosemide with antihypertensives and especially ACE inhibitors since these combinations can result in sudden and profound hypotension and renal toxicity. Low-dose dopamine infusion has been suggested as an alternative to high-dose furosemide infusion and may cause less toxicity. In a study¹³ in patients with severe refractory heart failure given optimal therapy with ACE inhibitors, oral diuretics, nitrates, and digoxin, additional therapy with low-dose intravenous dopamine (4 micrograms/kg per minute) and low-dose oral furosemide (80 mg daily) was as effective as intravenous high-dose furosemide (10 mg/kg daily) but caused less hypokalaemia and renal impairment. Use of intravenous hypertonic saline has also been reported¹⁴ to augment the effect of furosemide.

For the suggestion that torasemide may be a better choice of loop diuretic in patients with heart failure see p.1554.

1. Lawson DH, et al. Continuous infusion of frusemide in refractory oedema. *BMJ* 1978; 2: 476.

2. O'Rourke MF, et al. High-dose furosemide in cardiac failure. *Arch Intern Med* 1984; 144: 2429.

3. Gerlag PGG, van Meijel JHM. High-dose furosemide in the treatment of refractory congestive heart failure. *Arch Intern Med* 1988; 148: 286-91.

4. Hattersley AT, et al. Home intravenous diuretic therapy for patient with refractory heart failure. *Lancet* 1989; i: 446.

5. Chaner KS, et al. Thiazides with loop diuretics for severe congestive heart failure. *Lancet* 1990; 335: 922-3.

6. Aravot DJ, et al. Oral metolazone plus frusemide for home therapy in patients with refractory heart failure. *Lancet* 1989; i: 727.

7. Friedland JS, Ledingham JGG. Oral metolazone plus frusemide for home therapy in patients with refractory heart failure. *Lancet* 1989; i: 727-8.

8. Oster JR, et al. Combined therapy with thiazide-type and loop diuretic agents for resistant sodium retention. *Ann Intern Med* 1983; 99: 405-6.

9. Nomura A, et al. Effect of furosemide in congestive heart failure. *Clin Pharmacol Ther* 1981; 30: 177-82.

All cross-references refer to entries in Volume A

10. Dzau VJ, Hollenberg NK. Renal response to captopril in severe heart failure: role of furosemide in natriuresis and reversal of hyponatremia. *Ann Intern Med* 1984; **100**: 777-82.
11. Hamilton RW, Buckalew VM. Sodium, water, and congestive heart failure. *Ann Intern Med* 1984; **100**: 902-4.
12. Waterer G, Donaldson M. High-dose furosemide for cardiac failure. *Lancet* 1995; **346**: 254.
13. Cotter G, et al. Increased toxicity of high-dose furosemide versus low-dose dopamine in the treatment of refractory congestive heart failure. *Clin Pharmacol Ther* 1997; **62**: 187-93.
14. Patena S, et al. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as a bolus, in refractory congestive heart failure. *Eur J Heart Fail* 2000; **2**: 305-13.

Hypercalcaemia. Hypercalcaemia (p.1813) usually results from an underlying disease and long-term management involves treating the cause. However, if significant symptoms are present, treatment is necessary to reduce plasma-calcium concentrations. This mainly involves rehydration, but loop diuretics such as furosemide have traditionally been used after rehydration to promote urinary calcium excretion, a practice that has been questioned.^{1,3} Drugs such as bisphosphonates that inhibit bone resorption are now generally considered first-line where specific therapy is warranted, although loop diuretics may still have a role in the prevention of fluid overload or heart failure. Licensed doses used for hypercalcaemia have ranged from 20 to 240 mg of furosemide daily, given intravenously.

1. LeGrand SB, et al. Narrative review. Furosemide for hypercalcaemia: an unproven yet common practice. *Ann Intern Med* 2008; **149**: 259-63.
2. Robey RB, et al. Does furosemide have a role in the management of hypercalcaemia? *Ann Intern Med* 2009; **150**: 146-7.
3. LeGrand SB. Does furosemide have a role in the management of hypercalcaemia? *Ann Intern Med* 2009; **150**: 147.

Obstructive airways disease. In patients with asthma, furosemide given by oral inhalation has been found to protect against bronchoconstriction induced by exercise¹ and external stimuli,^{2,3} although it did not improve bronchial hyperresponsiveness in a 4-week study⁴ and provided no additional benefit when added to salbutamol for the treatment of acute asthma in a small study in children.⁵ Mechanisms have been suggested for the protective effect of furosemide, including inhibition of electrolyte transport across epithelium, inhibition of inflammatory mediators, or an effect on mast cell function.⁶ The potential for clinical applications remains unclear⁶ and furosemide is not a part of the accepted schedules for the treatment of asthma (p.1220).

Small studies in patients with chronic obstructive pulmonary disease have reported improvements in dyspnoea^{1,8} and exercise capacity⁹ with inhaled furosemide.

Inhaled furosemide has also been used to relieve dyspnoea in patients with terminal cancer.⁹

1. Munyari P, et al. Inhaled furosemide and exercise-induced bronchoconstriction in children with asthma. *Thorax* 1995; **50**: 677-9.
2. Bianco S, et al. Protective effect of inhaled furosemide on allergen-induced early and late asthmatic reactions. *N Engl J Med* 1989; **321**: 1069-73.
3. Seidenberg J, et al. Inhaled furosemide against cold air induced bronchoconstriction in asthmatic children. *Arch Dis Child* 1992; **67**: 214-17.
4. Yates DH, et al. Effect of acute and chronic inhaled furosemide on bronchial hyperresponsiveness in mild asthma. *Am J Respir Crit Care Med* 1995; **152**: 2173-5.
5. González-Sánchez R, et al. Furosemide plus albuterol compared with albuterol alone in children with acute asthma. *Allergy Asthma Proc* 2002; **23**: 181-4.
6. Floreani AA, Rennard SI. Experimental treatments for asthma. *Curr Opin Pulm Med* 1997; **3**: 30-41.
7. Ong K-C, et al. Effects of inhaled furosemide on exertional dyspnoea in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; **169**: 1028-33.
8. Jensen D, et al. Mechanisms of dyspnoea relief and improved exercise endurance after furosemide inhalation in COPD. *Thorax* 2008; **63**: 606-13.
9. Kallet RH. The role of inhaled opioids and furosemide for the treatment of dyspnoea. *Respir Care* 2007; **52**: 900-10.

Patent ductus arteriosus. The usual initial treatment for a haemodynamically significant ductus is reduction of fluid intake, correction of anaemia, support of respiration, and giving a diuretic. If that fails to control symptoms then indomethacin is generally given to promote closure of the ductus (see p.71).

Furosemide is often the diuretic chosen. It is effective and widely used but there has been concern that it might delay closure (and even increase the incidence of patent ductus arteriosus in infants treated for respiratory distress syndrome—see Effects in Infants and Neonates under Adverse Effects, above). A systematic review¹ of those treated for patent ductus concluded that this did not seem to be the case, and that the diuretic might reduce adverse renal effects of indomethacin; however, the evidence for this was limited and it was felt that there was not enough evidence to support the use of furosemide in infants treated with indomethacin.

1. Brion LP, Campbell DE. Furosemide for prevention of morbidity in indomethacin-treated infants with patent ductus arteriosus. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley, 2001 (accessed 12/07/05).

Raised intracranial pressure. Osmotic diuretics such as mannitol are first-line drugs for the management of raised intrac-

ranial pressure (p.1300) but loop diuretics such as furosemide may be used as adjuncts.

Tinnitus. Furosemide is one of many drugs that have been tried in tinnitus (p.2027), but although reported to be effective in some patients, it is rarely used because of problems with adverse effects.

Preparations

BP 2010: Co-amlofurose Tablets; Furosemide Injection; Furosemide Tablets; **USP 33:** Furosemide Injection; Furosemide Oral Solution; Furosemide Tablets.

Proprietary Preparations (details are given in Volume B)

Arg.: Errolon; Fabofurox; Frequental; Furagrand; Funtal; Furix; Fursemida; Furtenk; Kolkini; Lasix; Nurbian; Retep; **Austral.:** Fursehexal; Furisid; Lasix; Uremide; Urex; **Austria:** Fural; **Bulg.:** Furohexal; Furon; Furostad; Lasix; **Belg.:** Docufurose; Furtopur; Lasix; **Braz.:** Diuremida; Diureti; Diurix; Fluxil; Furesin; Furosan; Furosecord; Furosem; Furoseri; Furosetron; Furosi; Furozic; Fursemida; Lasix; Neosemid; Normotensor; Royelan; Urasic; **Canad.:** Lasix; Novo-Semide; **Chile:** Asax; **Cz.:** Dryptal; Furanthril; Furon; Furorese; Lasix; **Denn.:** Diuralt; Fureset; Furix; Lasix; **Fin.:** Furesis; Furamin; Lasix; Vesic; **Fr.:** Lasilix; **Ger.:** Diurapid; durafurid; Furanthril; Furon; Furo-Puren; Furobeta; Furogamma; Furomed; Furorese; Furosal; Fused; Ju-furix; Lasix; **Gr.:** Fudesic; Furanthril; Hydroflux; Lasix; Riomid; Semid; **Hong Kong:** CP-Furo; Diurex; Lasix; Naqua; Urex; **Hung.:** Furon; Huma-Semide; **India:** Furumex; Furusex; Frusac; Lasix; **Indon.:** Cetastix; **Israel:** Diuref; Edemin; Fasic; Furosi; Impugan; Lasix; Nalcex; Silax; Urex; **Irl.:** Fruside; Lasix; **Israël:** Fused; Miphar; **Ital.:** Lasix; **Malaysia:** Dirine; Furmed; Lasix; Rastio; Supinchor; **Mex.:** Biomiser; Butosal; Diuressel; Edenol; Furon; Furorjet; Henalex; Klimy; Lasix; Luzamida; Osemin; Silectofur; Zafimida; **Neth.:** Lasilettex; Lasix; **Norw.:** Diuralt; Furon; Lasix; **NZ:** Diurium; Furon; **Philipp.:** Diuralt; Diupres; Edemann; Flexamide; Fremid; Fretic; Frusma; Furide; Furorcan; Fusimex; Lasix; Pharmix; Pismor; Rofunil; **Port.:** Aquedux; Lasix; Naqua; **Rus.:** Lasix (Лазикс); **S.Afr.:** Aquand; Beunres; Lasix; Puresis; Uretic; **Singapore:** Dirine; Furmed; Lasix; **Spain:** Seguri; **Swed.:** Furic; Impugan; Lasix; **Switz.:** furo-basan; Furozic; Furor; Impugan; Lasix; Oedemex; **Thail.:** Aldic; Dirine; Femide; Frusil; Furidine; Furitic; Furide; Furine; Furmed; Furumide; Furozide; Fursemide; H-Mide; Hawkimide; Impugan; Lasix; Lasix; Proxis; Rosemide; Urasin; **Turk.:** Desal; Furomid; Lasix; Lasix; Ureux; **UAE:** Salurin; **UK:** Froop; Frusil; Frusil; Lasix; Rused; **Ukr.:** Lasix (Лазикс); **USA:** Lasix; **Venez.:** Biosemide; Edemin; Fromil; Indens; Lasix; Lufuro; Nacua; Resimide; Salca; Terysol.

Multi-ingredient: **Arg.:** Aldactone-D; Diflux; Errolon A; Furdirent; Lasilacton; Lasixide; Nurbian A; **Austria:** Furo-Aldopur; Furo-Spirobene; Furo-lacton; Hydrotrix; Lasilacton; Lasitace; Spirocomp; **Belg.:** Frusamil; **Braz.:** Diurana; Diurisa; Furosemide Composto; Hidrion; Lasilactona; **Chile:** Furdirent; Hidrium; Hidropid; **Cz.:** Spiro Compositum; **Denn.:** Frusamil; **Fin.:** Furesis comp; **Fr.:** Aldalic; Logirene; **Ger.:** Betasemid; Diaphal; durasipron-comp; Furo-Aldopur; Furosem Comp; Hydrotrix; Oxyrol Lasix; Spiro comp; Spiro-D; **Gr.:** Frumil; **India:** Diucontin-K; Frumil; Lasilactone; Spiromide; **Irl.:** Diuclide-K; Continus; Fur-Co; Frumil; **Ital.:** Fluss 40; Lastone; Spilur; **Mex.:** Lasilacton; **NZ:** Frumil; **Philipp.:** Diuclide-K; **Spain:** Salcur; **Switz.:** Frumil; Furcombin; Furospir; Lasilactone; **UK:** Andit; Froop Comp; Fur-Co; Frumil; Frusene; Komil; Lasilacton; Lasolide; **Venez.:** Furdirent.

Gallopamil Hydrochloride (BAN, rINN)

D-600 (gallopamil); Gallopamil, Chlorhydrate de; Gallopamilhydrochlorid; Gallopamil-Hydrochloridum; Gallopamilhydrochloridi; Hydrochloruro de gallopamil; Methoxyverapamil Hydrochloride. 5-[N-(3,4-Dimethoxyphenethyl)-N-methylamino]-2-(3,4,5-trimethoxyphenyl)-2-isopropylvaleronitrile hydrochloride.

Галлопамин Гидрохлорид

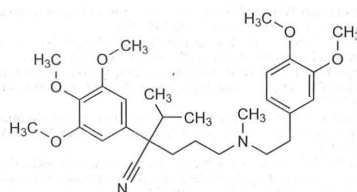
C₂₈H₄₀N₂O₅·HCl = 521.1.

CAS — 16662-47-8 (gallopamil); 16662-46-7 (gallopamil hydrochloride).

ATC — C08DA02.

ATC Vet — QC08DA02.

UNII — VT4VR32A0T.



(gallopamil)

Profile

Gallopamil is a calcium-channel blocker (see p.1270) with antiarrhythmic activity and is chemically related to verapamil. It is used in the management of angina pectoris (p.1273), cardiac arrhythmias (p.1277), and hypertension (p.1290). Gallopamil hydrochloride is given orally in doses of 25 to 50 mg every 6 to 12 hours up to a maximum total dose of 200 mg daily. Modified-release preparations are also available and are given once or twice daily in similar total daily doses.

General references.

1. Brogden RN, Benfield P. Gallopamil: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in ischaemic heart disease. *Drugs* 1994; **47**: 93-115.

Preparations

Proprietary Preparations (details are given in Volume B)

Austria: Procorum; **Ger.:** Gallobeta; Procorum; **Hung.:** Procorum; **Ital.:** Algor; Procorum; **Mex.:** Procorum; **Philipp.:** Procorum; **Thail.:** Procorum.

Gemfibrozil (BAN, USAN, rINN)

CI-719; Gemfibrosilli; Gemfibrozilo; Gemfibrozilum; Gemfibrozyl. 2,2-Dimethyl-5-(2,5-xylyloxy)valeric acid.

Гемфиброзил

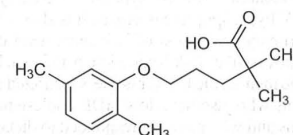
C₁₅H₂₂O₅ = 250.3.

CAS — 25812-30-0.

ATC — C10AB04.

ATC Vet — QC10AB04.

UNII — Q8X02027X3.



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

Ph. Eur. 6.8 (Gemfibrozil). A white or almost white, waxy, crystalline powder. M.p. 58° to 61°. Practically insoluble in water; freely soluble in dehydrated alcohol and in methyl alcohol; very soluble in dichloromethane. Protect from light.

USP 33 (Gemfibrozil). A white waxy crystalline solid. M.p. 58° to 61°. Practically insoluble in water; soluble in alcohol, in methyl alcohol, and in chloroform. Store in airtight containers.

Adverse Effects and Precautions

As for Bezafibrate, p.1356.

Incidence of adverse effects. In the Helsinki Heart Study,¹ 11.3% of 2051 patients taking gemfibrozil reported various moderate to severe upper gastrointestinal tract symptoms during the first year of treatment compared with 7% of 2030 patients taking placebo. No differences were seen between gemfibrozil and placebo groups in haemoglobin concentrations, urinary-protein, or urinary-sugar concentrations.

There was no significant difference in the total number of cancers between the gemfibrozil and placebo groups nor in the number of operations for gallstones or for cataract surgery. A higher number of deaths in the gemfibrozil group was mainly due to accident or violence and intracranial haemorrhage.

A follow-up study² reported that gastrointestinal symptoms remained more common in patients taking gemfibrozil. Although there was no significant difference between the gemfibrozil and placebo groups cholecystectomies were consistently more common in those receiving gemfibrozil during the entire 8.5-year observation period. Cancer occurred equally in both groups, but there was increased mortality attributable to cancer in the gemfibrozil group, mainly during the last 1.5 years of follow-up; this difference was no longer apparent after 18 years.³

1. Frick MH, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidaemia: safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987; **317**: 1237-45.
2. Huttunen JK, et al. The Helsinki Heart Study: an 8.5-year safety and mortality follow-up. *J Intern Med* 1994; **235**: 31-9.
3. Tenkanen L, et al. Gemfibrozil in the treatment of dyslipidaemia: an 18-year mortality follow-up of the Helsinki Heart Study. *Arch Intern Med* 2006; **166**: 743-8.

Effects on the skin. Psoriasis was exacerbated in a patient within 2 weeks of starting gemfibrozil therapy and recurred when gemfibrozil was subsequently reintroduced.¹

1. Fisher DA, et al. Exacerbation of psoriasis by the hypolipidemic agent, gemfibrozil. *Arch Dermatol* 1988; **124**: 854-5.

Interactions

As for Bezafibrate, p.1357.

Gemfibrozil is an inhibitor of several cytochrome P450 isoenzymes, including CYP2C8, CYP2C9, CYP2C19, and CYP1A2 and may increase the plasma concentration of drugs metabolised by these isoenzymes; it also inhibits some UDP-glucuronosyltransferases. Increased plasma concentration of bexarotene (see p.750), pioglitazone (see p.495), and rosiglitazone (see p.499) have been reported with gemfibrozil, and use of gemfibrozil in patients receiving repaglinide is contraindicated due to the risk of serious hypoglycaemia (see p.497).

The symbol † denotes a preparation no longer actively marketed

tal; Caltrate Plus; **Port.**: Caltrate Plus Mastigavel; Caltrate Plus; Selenium-ACE Extra; Tot'Hema; **Rus.**: Calcein (Кальцеин); Calcein Advance (Кальцеин Адванс); Tot'Hema (Тотема); **S.Afr.**: Dr Williams Pink Pills; Ferrous Sulphate Compound; ProFLEX; **Singapore.**: Arthro-Flex; Caltrate Plus; Eviprost; Neogobion; Procosa II; Rullex; Sangobion; **Thai.**: Caltrate Plus; Calvin Plus; Glufex-C; **Turk.**: Eser Metaller; Ultimate; **UK.**: Calcein; Caltrate Plus; Joint Action; Ostron; **Ukr.**: Calcein (Кальцеин); Calcein Advance (Кальцеин Адванс); Vimifor Multivitamin with Beta-Carotene (Віміфор Мультивітамін З Бета-каротином); **USA.**: Caltrate Plus; Gro-Man-Zin; **Venez.**: Osozin; Oxi-Cell Plus; Vitalex.

Homoeopathic: **Canada.**: Arth-B Oligocant; Formula DE 226; O'Print; Sinuspar; **Fr.**: Silicea Complexe No 11; Sinuspar; Uranium Compose; Vox-rax; **Ger.**: Drufusan N; NeyArthros-Liposome (Revitorgan Lp Nr 83); NeyArthrosome (Revitorgan-Dilution); Nieren-Elixer ST; **Switz.**: Sinuspar.

Medium-chain Triglycerides

Keskikettäketjuiset tydytynneet triglyseridit; Triacylglyceroly střední nasycené; Triglyceridai, vidutines grandinės; Trigliceridek, közepes szénláncú zsírsavaké; Triglicéridos de cadena media; Triglycerida saturata media; Triglycerider, medellängkedjiga; Triglicérides à chaîne moyenne.

Среднецепочечные Триглицериды

UNII — C9H2L21V7U.

Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF*.

Ph. Eur. 6.8 (Triglycerides, Medium-chain). The fatty acids are obtained from the oil extracted from the hard, dried fraction of the endosperm of *Cocos nucifera* or from the dried endosperm of *Elaeis guineensis*. They consist of a mixture of triglycerides of saturated fatty acids, mainly of octanoic acid and of capric acid ($C_{10}H_{20}O_2 = 172.3$). They contain not less than 95% of saturated fatty acids with 8 and 10 carbon atoms. A colourless or slightly yellowish, oily liquid. Practically insoluble in water; miscible with alcohol, with dichloromethane, with petroleum spirit, and with fatty oils. Store in well-filled containers. Protect from light. **USNF 28** (Medium-Chain Triglycerides). They are obtained from the oil extracted from the hard, dried fraction of the endosperm of *Cocos nucifera* or from the dried endosperm of *Elaeis guineensis*. They consist of a mixture of triglycerides of saturated fatty acids, mainly of octanoic acid and of capric acid ($C_{10}H_{20}O_2 = 172.3$). They contain not less than 95% of saturated fatty acids with 8 and 10 carbon atoms. A colourless or slightly yellowish, oily liquid. Practically insoluble in water; miscible with alcohol, with dichloromethane, with petroleum spirit, and with fatty oils. Store in airtight containers at a temperature not exceeding 25°. Protect from light.

Profile

Medium-chain triglycerides are used for enteral and parenteral nutrition (p.2080) in conditions associated with malabsorption of fat, such as cystic fibrosis, enteritis, and steatorrhea, and after intestinal resection. Medium-chain triglycerides are more readily hydrolysed than long-chain triglycerides and are not dependent upon biliary or pancreatic secretions for absorption from the gastrointestinal tract. They provide 35 kJ (8.3 kcal) per g. They do not provide essential fatty acids.

Medium-chain triglycerides have also been used as bases for pharmaceutical preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Arg.: Teceeme; **Austral.**: Liqueur; MCT Oil; **Denm.**: MCT Oil; Liqueur; MCT Oily; **Fr.**: Liqueur; **Gr.**: MCT Oil; **Hung.**: Structolipid; **Ir.**: Liqueur; **Israel.**: MCT; **Ital.**: MCT; Mytic 810; **NZ.**: Liqueur; MCT Oil; **Port.**: MCT Oil; **UK.**: Alernibol D; Liqueur; MCT Oil; **USA.**: MCT.

Multi-ingredient: **Arg.**: Lipofundin MCT/LCT-E; Lipofundin MCT/LCT; **Austral.**: Caprilon; MCT Duocal; Visine Professional; **Austria.**: Lipidem; Lipofundin MCT; SMOFlipid; Structolipid; **Belg.**: Medialipide; **Chile.**: Lipofundin MCT/LCT; Lipovenos MCT/LCT; **Cz.**: Lipofundin MCT/LCT; Lipopus; Nutriflex Lipid; SMOFkaben; SMOFlipid; Structolipid; **Denm.**: Liqueur; MCT Duocal; SMOFlipid; Structolipid; **Fin.**: Lipoplus; Nutriflex Lipid; SMOFlipid; Structolipid; Vasolipid; **Fr.**: Lipidem; Lipocit; Medialipide; Mednutriflex Lipide G; Nutriflex Lipide; Structolipide; **Ger.**: Gleitgelen; Lipofundin MCT; Lipovenos MCT; Nutriflex Lipid; SMOFlipid; Visine Trockene Augen; **Gr.**: Lipofundin MCT/LCT; Lipopus; SMOFlipid; Structolipid; **Hong Kong.**: Lipofundin MCT/LCT; Nutriflex Lipid; **Hung.**: Lipofundin MCT; Lipovenos PLR; SMOFlipid; **Indon.**: Hepabion; Lipimix; Lipofundin MCT/LCT; **Ir.**: Caprilon; Lipidem; Lipofundin MCT/LCT; MCT Duocal; Nutriflex Lipid; SMOFkaben; SMOFlipid; Structolipid; **Israel.**: Lipofundin MCT/LCT; **Ital.**: Caprilon; Dicovit; Dicovit K; Lipidem; Lipofundin MCT; Nutripen Lipid; Nutrilip Lipid; Nutrispecial Lipid; SMOFlipid; Structolipid; Visine Dry Eyes; **Mex.**: Lipofundin MCT/LCT; Lipovenos MCT; **Neth.**: Lipofundin MCT/LCT; Lipopus; Nutriflex Lipid; SMOFlipid; Structolipid; **Norw.**: Nutriflex Lipid; SMOFlipid; Structolipid; Vasolipid; **NZ.**: Structolipid; **Pol.**: Lipofundin MCT/LCT; SMOFkaben; SMOFlipid; **Port.**: Lipofundin MCT/LCT; Lipopus; Nutribrav; SMOFkaben; SMOFlipid; Structolipid; **Rus.**: Lipofundin MCT/LCT (Липофундин МСТ/АСТ); Lipoplus (Липоплюс); SMOFlipid (СМОФлипод); **S.Afr.**: Lipofundin MCT/LCT; **Spain.**: Lipofundin MCT/LCT; Lipoplus; Nutriflex Lipid; SMOFlipid; Structolipid; **Swed.**: Lipoplus; Nutriflex Lipid; SMOFlipid; Structolipid; Vasolipid; **Switz.**: Lipofundin MCT/LCT; Nutriflex Lipid; SMOFlipid; Structolipid; **Thai.**: Lipofundin MCT/LCT; MCT Duocal; Structolipid; **Turk.**: Lipofundin MCT/LCT; **UK.**: Caprilon; Imudem; Lipidem; Lipofundin MCT/LCT; MCT Duocal; Nutriflex Lipid; SMOFlipid; Structolipid; **Ukr.**: Lipofundin MCT/LCT (Липофундин МСТ/АСТ); **Venez.**: Lipofundin MCT/LCT; Propof.

The symbol † denotes a preparation no longer actively marketed

Molybdenum

Molibdeno; Molibdenum; Molybdän; Molybdene.

Молибден

Mo = 95.96.

UNII — 81AH48963U.

Ammonium Molybdate

Amonowy molibdenian; Molibdato de amonio. Hexaammonium molybdate tetrahydrate.

Молибдат Аммония; Молибденовокислый Аммоний

(NH₄)₆Mo₇O₂₄·4H₂O = 1236.0.

CAS — 12054-85-2.

UNII — OG154X474 (ammonium molybdate tetrahydrate); 21Y68178E (anhydrous ammonium molybdate).

Pharmacopoeias. In *US*.

USP 33 (Ammonium Molybdate). Colourless or slightly greenish or yellowish crystals. Soluble in water; practically insoluble in alcohol. Store in airtight containers.

Sodium Molybdate

Molibdato de sodio; Molybdenan sodný dihydrát; Natrii molybdatas dihydricus; Natrio molibdatas dihidratas; Natrium-molibdenát-dihidrátt; Natriummolybdaattidihdraatti; Natriummolybdatdihydrat; Sodium (molybdate de) dihydraté; Soda molibdenian.

Молибдат Натрия; Молибденовокислый Натрий

Na₂MoO₄·2H₂O = 242.0.

UNII — 9480AQ081I.

Pharmacopoeias. In *Eur.* (see p.vii). *Ger.* also includes a monograph for the anhydrous substance.

Ph. Eur. 6.8 (Sodium Molybdate Dihydrate). A white or almost white powder or colourless crystals. Freely soluble in water.

Adverse Effects

Very high intakes of molybdenum, and associated increases in xanthine oxidase activity, may result in hyperuricaemia, and possibly gout. Molybdenum intoxication may impair the utilisation of copper.

Uses and Administration

Molybdenum is an essential trace element and small amounts, in the form of ammonium molybdate or sodium molybdate, are sometimes added to solutions for TPN. A suggested dose is about 20 to 120 micrograms (0.2 to 1.2 micromoles) elemental molybdenum daily.

Ammonium molybdate is used in veterinary medicine to treat copper poisoning in sheep.

Human requirements. In the UK neither a reference nutrient intake (RNI) nor an estimated average requirement (EAR) (see p.2082) has been set for molybdenum although a safe intake was believed to be between 50 and 400 micrograms (0.5 and 4 micromoles) daily for adults.¹ In the USA, the recommended dietary allowance is 45 micrograms daily for adults.² The tolerable upper intake level is 2 mg daily.² WHO make the suggestion that the adult basal requirement for molybdenum could be about 25 micrograms daily,³ corresponding to approximately 400 nanograms/kg.

Foods contributing to dietary molybdenum include milk, beans, breads, and cereals; however, extreme regional variations occur in molybdenum contents of food crops due to soil differences.

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc*. Washington DC: National Academy Press, 2001. Also available at: <http://www.nap.edu/openbook.php?isbn=0309072794> (accessed 21/07/08).
3. WHO. Molybdenum. In: *Trace elements in human nutrition and health*. Geneva: WHO, 1996; 144–54.

Preparations

USP 33: Ammonium Molybdate Injection; Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Oil- and Water-soluble Vitamins with Minerals Tablets; Trace Elements Injection; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Proprietary Preparations (details are given in Volume B)

Fr.: Molybdeno Injectabile; **USA:**: Molyphen.

Multi-ingredient: **Canada.**: T-O-S; **Hung.**: Humet-R; Kinder Biovitaf; **Thai.**: Ferrovit; **Ukr.**: Vimifor Multivitamin with Beta-Carotene (Віміфор Мультивітамін З Бета-каротином).

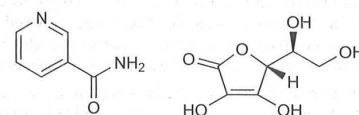
Nicotinamide Ascorbate (BANM, rINN)

Ascorbató de nicotinamida; Nicotinamide Ascorbate; Nicoscorbine; Nicotinamide, Ascorbate de; Nicotinamidi Ascorbas.

Никотинамида Аскорбат

C₁₂H₁₄N₂O₇ = 298.2.

CAS — 1987-71-9.



Profile

Nicotinamide ascorbate is a complex of nicotinamide (p.2117) with ascorbic acid (p.2145) that is used in multivitamin preparations. It has also been given with betaine glucuronate and di-amine glucuronate for liver disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient: **Hong Kong:** Jetepear; **Malaysia:** Jetepear; **Philipp.**: Jetepear; **Singapore:** Jetepear.

Nicotinic Acid (BAN, rINN)

375; Acide nicotinique; Ácido nicotínico; Acidum nicotinicum; Kwas nikotinowy; Kyselina nikotinová; Niacin; Niacina; Nikotiini-happo; Nikotinik Asit; Nikotino rūgštis; Nikotinsäure; Nikotinsav; Nikotinsyra. Pyridine-3-carboxylic acid.

Никотиновая Кислота

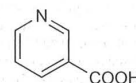
C₆H₅NO₂ = 123.1.

CAS — 59-67-6.

ATC — C04AC01; C10AD02.

ATC Vet — QC04AC01; QC10AD02.

UNII — 2679MF687A.



NOTE. Some published sources use the term niacin as a generic term to include both nicotinic acid and nicotinamide.

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

Ph. Eur. 6.8 (Nicotinic Acid). A white or almost white, crystalline powder. Sparingly soluble in water; soluble in boiling water and in boiling alcohol. It dissolves in dilute solutions of alkali hydroxides and carbonates. Protect from light.

USP 33 (Niacin). White crystals or crystalline powder, odourless or has a slight odour. Soluble 1 in 60 of water; freely soluble in boiling water, in boiling alcohol, and in solutions of alkali hydroxides and carbonates; practically insoluble in ether.

Nicotinamide (BAN, rINN)

Niacinamide; Nicotinamida; Nicotinamidum; Nicotinic Acid Amide; Nicotylamide; Nicotiniamid; Nicotinamid; Nikotinamidas; Nikotinamid; Vitamin B₃; Vitamin PP; Vitamina B₃; Vitamina PP; Pyridine-3-carboxamide.

Никотинамид

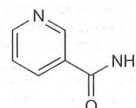
C₆H₆N₂O = 122.1.

CAS — 98-92-0.

ATC — A11HA01.

ATC Vet — QA11HA01.

UNII — 25X5118RD4.



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

Ph. Eur. 6.8 (Nicotinamide). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water and in dehydrated alcohol. A 5% solution in water has a pH of 6.0 to 7.5.

USP 33 (Niacinamide). A white crystalline powder, odourless or practically so. Soluble 1 in 1.5 of water, 1 in 10 of boiling water, and 1 in 5.5 of alcohol; soluble in glycerol. Its solutions are neutral to litmus. Store in airtight containers.

Adverse Effects and Treatment

Nicotinic acid has a vasodilator action and when given orally or by injection in therapeutic doses it may cause flushing, a sensation of heat, faintness, and a pounding in the head. Flushing may be accompanied by tingling,

headache, dizziness, tachycardia, palpitations, dyspnoea, sweating, chills, or oedema. These symptoms are transient and various strategies have been proposed to reduce them (see Incidence of Adverse Effects, below). Nicotinamide does not have a vasodilator action.

Other adverse effects that have been reported, especially after high doses of nicotinic acid, include dryness of the skin, pruritus, hyperpigmentation, rash, cramps, diarrhoea, nausea and vomiting, anorexia, activation of peptic ulcer, eye disorders including cystoid macular oedema and toxic amblyopia, decrease in glucose tolerance, hyperglycaemia, and hyperuricaemia. Most of these effects subside on withdrawal of the drug. Nicotinic acid has been associated with abnormal liver function tests and jaundice. Increases in liver transaminases are generally reversible on stopping treatment. Hypophosphataemia, a reduction in platelet counts, prolongation of prothrombin time, arrhythmias, and hypersensitivity reactions including angioedema have also been reported. Insomnia, myalgia, hypotension, and rhinitis may occur rarely.

Topical nicotinamide may cause dryness of the skin and, less frequently, pruritus, erythema, burning sensation, and irritation. Frequency of application should be reduced if these effects occur.

References.

1. Guyton JR, Bays HE. Safety considerations with niacin therapy. *Am J Cardiol* 2007; **99** (suppl 1): S22–S31.

Incidence of adverse effects. Nicotinic acid produces frequent adverse effects, but they are not usually serious, tend to decrease with time, and some can be minimised by following appropriate instructions for use.^{1,2} Dermal and gastrointestinal reactions are most common. Truncal and facial flushing are reported in 90 to 100% of treated patients in large clinical studies; they appear to be prostaglandin-mediated and can be reduced with aspirin 75 mg or 325 mg given shortly before the nicotinic acid, or simply by giving nicotinic acid with food, and by starting therapy with a low dose and gradually increasing this. It may also help to avoid eating spicy foods or drinking hot drinks or alcohol at the same time as taking nicotinic acid. Flushing may be less common with modified-release formulations;² furthermore, an analysis of serious adverse events reported to the FDA suggested that the incidence of such effects (including effects on the liver) with modified-release preparations of nicotinic acid was about one-sixth of that with conventional formulations.³ A modified-release preparation containing nicotinic acid with laropiprant, a prostaglandin D₂ receptor antagonist that inhibits nicotinic-acid induced flushing, is also available, see below. Adverse effects reported with a combined formulation of modified-release nicotinic acid with lovastatin were comparable to those with either drug alone.

1. Knodel LC, Talbert RL. Adverse effects of hypolipidaemic drugs. *Med Toxicol* 1987; **2**: 10–32.

2. American Society of Health-System Pharmacists, ASHP therapeutic position statement on the safe use of niacin in the management of dyslipidemias. *Am J Health-Syst Pharm* 1997; **54**: 2815–19.

3. Alsheikh-Ali AA, Karas RH. The safety of niacin in the US Food and Drug Administration adverse event reporting database. *Am J Cardiol* 2008; **101** (suppl): 9B–13B.

Effects on the eyes. Retrospective survey of hyperlipidaemic patients suggested that dry eyes (sicca syndromes), blurred vision, and swollen eyelids might be associated with nicotinic acid therapy in some patients.¹ The effects appeared to be dose-related and reversible. In 2 patients treatment was stopped because of symptoms suggestive of cystoid macular oedema. Other cases of nicotinic acid maculopathy have been reported.^{2,3}

1. Fraunfelder FW, et al. Adverse ocular effects associated with niacin therapy. *Br J Ophthalmol* 1995; **79**: 54–6.

2. Callanan D, et al. Macular edema associated with nicotinic acid (niacin). *JAMA* 1998; **279**: 1702.

3. Sporn MJ, et al. Optical coherence tomography findings in nicotinic acid maculopathy. *Am J Ophthalmol* 2003; **135**: 913–14.

Effects on glucose tolerance. Nicotinic acid can reduce glucose tolerance, and this may be problematic in patients with diabetes mellitus,^{1,2} although it has been investigated in the prevention of diabetes mellitus (see below). A review³ of the effects of nicotinic acid on glucose control in patients with dyslipidaemia found that, although it is recognised that it can increase blood glucose concentrations, the effects were typically minor (about 4 to 5%) when given at daily doses of 2.5 g or less. In most patients with type 2 diabetes mellitus changes in blood glucose concentrations could be managed by adjusting antidiabetic therapy, and the cardiovascular benefits of nicotinic acid treatment might outweigh the risks.

1. American Society of Health-System Pharmacists, ASHP therapeutic position statement on the safe use of niacin in the management of dyslipidemias. *Am J Health-Syst Pharm* 1997; **54**: 2815–19.

2. Kreisberg RA. Niacin: a therapeutic dilemma—"one man's drink is another's poison". *Am J Med* 1994; **97**: 313–16.

3. Goldberg RB, Jacobson TA. Effects of niacin on glucose control in patients with dyslipidemia. *Mayo Clin Proc* 2008; **83**: 470–8.

Effects on the liver. Hepatotoxicity may occur with nicotinic acid.^{1,6} Significant elevations of liver enzymes are occasionally seen with nicotinic acid therapy. They are more common in patients given large dosage increases over short periods of time, and in patients treated with modified-release formulations. It has been suggested⁷ that since effects on liver function may in some instances lead to hepatic failure and are more common with modified-release dosage forms the use of crystalline immediate-release preparations should be preferred, a view shared by other commentators.⁸ However, although studies appear to confirm a more frequent association of hepatotoxicity with modified-release dosage forms,^{4,9,10} it should be borne in mind that these effects can also occur with the immediate-release preparations, especially at high doses. Some manufacturers of modified-release preparations have stated that cases of severe hepatotoxicity, including fulminant hepatic necrosis, have occurred when patients have substituted modified-release dosage forms for immediate-release crystalline preparations at equivalent doses. There is also a suggestion that not all modified-release preparations are alike in their effects.¹¹ For a study indicating a lower incidence of reported serious adverse effects in patients given modified-release rather than conventional formulations, see Incidence of Adverse Effects, above.

1. Henkin Y, et al. Rechallenge with crystalline niacin after drug-induced hepatitis from sustained-release niacin. *JAMA* 1990; **264**: 241–3.

2. Hodis HN. Acute hepatic failure associated with the use of low-dose sustained-release niacin. *JAMA* 1990; **264**: 181.

3. Etchason JA, et al. Niacin-induced hepatitis: a potential side effect with low-dose time-release niacin. *Mayo Clin Proc* 1991; **66**: 23–8.

4. Rader JJ, et al. Hepatic toxicity of unmodified and time-release preparations of niacin. *Am J Med* 1992; **92**: 77–81.

5. Coppola A, et al. Niacin-induced hepatotoxicity: unusual presentations. *South Med J* 1994; **87**: 30–2.

6. Gavalán JC, et al. Hepatitis inducida por niacina. *Med Clin (Barc)* 2002; **118**: 558.

7. Palumbo PJ. Rediscovery of crystalline niacin. *Mayo Clin Proc* 1991; **66**: 112–13.

8. Kreisberg RA. Niacin: a therapeutic dilemma—"one man's drink is another's poison". *Am J Med* 1994; **97**: 313–16.

9. McKenney JM, et al. A comparison of the efficacy and toxic effects of sustained- vs immediate-release niacin in hypercholesterolemic patients. *JAMA* 1994; **271**: 672–7.

10. Gray DR, et al. Efficacy and safety of controlled-release niacin in dyslipoproteinemic veterans. *Ann Intern Med* 1994; **121**: 252–8.

11. Lavie CJ, Milani RV. Safety and side-effects of sustained-release niacin. *JAMA* 1994; **272**: 513–14.

Effects on the muscles. Myopathy has been noted with nicotinic acid.^{1,2} Rhabdomyolysis has occurred when nicotinic acid was given with lovastatin (see Lipid Regulating Drugs, under Interactions of Simvastatin, p.1529). However, an analysis of adverse events reported to the FDA with a combination of modified-release nicotinic acid and lovastatin suggested the incidence was no higher than with either drug alone, see Incidence of Adverse Effects, above.

1. Litin SC, Anderson CF. Nicotinic-acid associated myopathy: a report of three cases. *Am J Med* 1989; **86**: 481–3.

2. Gharavi AG, et al. Niacin-induced myopathy. *Am J Cardiol* 1994; **74**: 841–2.

Hyperuricaemia. Nicotinic acid decreases urinary excretion of uric acid, which may result in elevation of serum uric acid and exacerbation of pre-existing gout.¹

1. American Society of Health-System Pharmacists, ASHP therapeutic position statement on the safe use of niacin in the management of dyslipidemias. *Am J Health-Syst Pharm* 1997; **54**: 2815–19.

Precautions

Liver function should be tested before starting treatment with nicotinic acid, every 6 to 12 weeks for the first year, and periodically thereafter. A persistent increase in transaminases of 3 or more times the upper limit of normal requires a reduction in dose or treatment to be stopped. Nicotinic acid should not be used in patients with significant hepatic impairment, and treatment should be closely monitored in those with jaundice or other hepato-biliary disorders. Modified-release preparations should not be substituted for equivalent doses of immediate-release crystalline nicotinic acid preparations, as cases of severe hepatotoxicity, including fulminant hepatic necrosis, have occurred.

Caution is required when using nicotinic acid in patients with active peptic ulcer disease or acute coronary syndrome, patients with or predisposed to gout, or in those who consume large amounts of alcohol. Nicotinic acid and its metabolites are excreted via the kidneys and caution is required in patients with renal dysfunction.

Patients with diabetes mellitus should be monitored closely when taking nicotinic acid as increases in fasting blood glucose have occurred.

Interactions

Although some evidence suggests that combinations of nicotinic acid and statins can be given safely (see Incidence of Adverse Effects, above), there may be an increased risk of myopathy or rhabdomyolysis (see Lipid Regulating Drugs, under Interactions of Simvastatin, p.1529). Nicotinic acid may increase the requirements for insulin or oral hypoglycaemics. Aspirin may reduce the clearance of nicotinic acid. *In vitro* studies suggest that colestipol and colestyramine may reduce the availability of nicotinic acid, and some licensed product information recommends an interval of at least 4 to 6 hours between giving nicotinic acid and bile-acid binding resins.

Antiepileptics. For the effect of nicotinamide on carbamazepine, see Vitamins, p.518.

Nicotine. A patient started to have flushing and dizziness after her usual doses of nicotinic acid when transdermal nicotine patches were added to her therapy.¹ She had experienced such reactions 3 years previously on starting nicotinic acid therapy, but not since, and it was suggested that on this occasion an interaction might have been responsible.

1. Rockwell KA. Potential interaction between niacin and transdermal nicotine. *Ann Pharmacother* 1993; **27**: 1283–4.

Pharmacokinetics

Nicotinic acid and nicotinamide are readily absorbed from the gastrointestinal tract after oral doses and widely distributed in the body tissues. Nicotinic acid appears in breast milk. The main route of metabolism is their conversion to *N*-methylnicotinamide and the 2-pyridone and 4-pyridone derivatives; nicotinic acid is also formed. Small amounts of nicotinic acid and nicotinamide are excreted unchanged in urine after therapeutic doses; however the amount excreted unchanged is increased with larger doses.

References.

1. Pieper JA. Overview of niacin formulations: differences in pharmacokinetics, efficacy, and safety. *Am J Health-Syst Pharm* 2003; **60** (Suppl 2): S9–14.

Human Requirements

The daily human requirement of nicotinic acid, though not definitely known, is probably about 15 to 20 mg. Yeast, meat, fish, potatoes, legumes, and wholemeal cereals are good sources of nicotinic acid and nicotinamide. However they may be present in a bound, unabsorbable form in cereals, especially maize. Nicotinic acid can also be obtained from the conversion of tryptophan in the body, 60 mg of dietary tryptophan being considered equivalent to 1 mg of dietary nicotinic acid, so requirements are influenced by dietary protein intake and if protein intake is adequate there is little need for any preformed vitamin in the diet. There is generally little loss of nicotinic acid from foods during cooking.

UK and US recommended dietary intake. In the UK dietary reference values (see p.2082) have been published for nicotinic acid¹ and in the USA recommended dietary allowances (RDAs) have been set.² In the UK the reference nutrient intake (RNI) is 6.6 mg niacin equivalent per 1000 kcal daily and the estimated average requirement (EAR) is 5.5 mg niacin equivalent per 1000 kcal daily for adult males and females. One niacin equivalent is equal to 1 mg of dietary nicotinic acid or 60 mg of dietary tryptophan. In the US the RDAs are also expressed in niacin equivalents and are 16 mg daily for adult males and 14 mg daily for adult females; the EAR is 12 mg daily in males and 11 mg daily in females. The tolerable upper intake level for adults is 35 mg daily.²

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects* 41. London: HMSO, 1991.

2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B₆, folate, vitamin B₁₂, pantothenic acid, biotin, and choline*. Washington, DC: National Academy Press, 2000. Also available at: <http://www.nap.edu/openbook.php?isbn=0309065542> (accessed 21/07/08)

Uses and Administration

Nicotinic acid and nicotinamide, the form that occurs naturally in the body, are water-soluble vitamin B substances that are converted to nicotinamide adenine dinucleotide (nadide, p.2579) and nicotinamide adenine dinucleotide phosphate (NADP). These coenzymes are involved in electron transfer reactions in the respiratory chain.

Nicotinic acid deficiency develops when the dietary intake is inadequate. Deficiency leads to the development of a syndrome known as pellagra, characterised by skin lesions, especially on areas exposed to sunlight, with hyperpigmentation and hyperkeratinisation. Other symptoms include diarrhoea, abdominal pain, glossitis, stomatitis, loss of appetite, headache, lethargy, and mental and neurological disturbances. Nicotinic acid deficiency may occur with other vitamin B-complex deficiency states, for example in alcoholism.

Nicotinic acid and nicotinamide are used in the treatment and prevention of **nicotinic acid deficiency**. Nicotinamide is preferred as it does not cause vasodilatation. They are usually given orally, the preferred route, but may also be given by the intramuscular route or by slow intravenous injection. Doses of up to 500 mg daily (of either compound) in divided doses have been recommended.

Nicotinic acid has been used for its **vasodilator** action in the treatment of a variety of disorders; its value is not considered to be established.

In high doses, nicotinic acid has beneficial effects on blood lipid profiles, and has been used, with dietary modification and often with other lipid regulating drugs, in **hyperlipidaemias** (see below). For the immediate-release preparations, an initial oral dose of 250 mg once daily is increased every 4 to 7 days until a dose of 1.5 to 2 g daily is reached or the desired effect is seen. If hyperlipidaemia is not controlled after 2 months at this dose, the dose can be increased at 2- to 4-week intervals to 3 g daily in 3 divided doses. Although US licensed product information suggests that doses up to 6 g daily may be required in some patients, the *National Heart, Lung, and Blood Institute* in the USA recommends a maximum dose of 4.5 g daily.

Alternatively, initial doses of 375 or 500 mg at night have been given as a modified-release preparation and gradually increased according to response to a maintenance dose of 1 to 2 g at bedtime. The daily dose should not be increased by more than 500 mg in any 4-week period.

A modified-release combination preparation containing nicotinic acid with laropirant (p.2555), a prostaglandin D₂ receptor 1 antagonist that inhibits nicotinic acid-induced flushing, may also be used. The combination preparation may be given orally in an initial dose of 1 g nicotinic acid/20 mg laropirant once daily, increased after 4 weeks to a maintenance dose of 2 g nicotinic acid/40 mg laropirant once daily; it should be taken with food in the evening or at bedtime.

Topical nicotinamide is used in the treatment of mild to moderate inflammatory **acne** (see below), typically as a 4% gel applied twice daily.

Nicotinamide has been shown to inhibit the destruction of pancreatic beta cells *in vitro* and is therefore being investigated in the prevention and treatment of type 1 **diabetes mellitus** (see below).

Acne. Topical nicotinamide may be used in the treatment of inflammatory **acne** (p.1717); nicotinamide 4% was as effective as clindamycin 1% when applied topically twice daily for 8 weeks.¹

1. Shalita AR, *et al.* Topical nicotinamide compared with clindamycin gel in the treatment of inflammatory acne vulgaris. *Int J Dermatol* 1995; 34: 434-7.

Diabetes mellitus. Nicotinic acid can affect glucose tolerance and should be used with care in established diabetes (see Effects on Glucose Tolerance, above). However, the drug has been used successfully in patients with diabetes. Nicotinamide has been reported to induce remission in patients with newly diagnosed type 1 diabetes mellitus (p.463), and may delay the onset of disease.^{1,2} However, a randomised study found modified-release nicotinamide at 1.2 g/m² daily (to a maximum of 3 g daily) to be ineffective in preventing the onset of diabetes mellitus in first-degree relatives of patients with the disease.³ Nicotinic acid can also raise high-density lipoprotein (HDL)-cholesterol concentrations (see below);^{4,5} changes in glucose tolerance were mild enough for the drug to be considered as an alternative to statins and fibrates in diabetic patients. For further discussion of the role of nicotinic acid in the management of dyslipidaemias in diabetic patients, see under Diabetic Complications, p.467.

1. Elliott RB, Chase HP. Prevention or delay of type 1 (insulin-dependent) diabetes mellitus in children using nicotinamide. *Diabetologia* 1991; 34: 362-5.

2. Pozzilli P, *et al.* Meta-analysis of nicotinamide treatment in patients with recent-onset IDDM. *Diabetes Care* 1996; 19: 1357-63.

3. European Nicotinamide Diabetes Intervention Trial Group. European Nicotinamide Diabetes Intervention Trial (ENDIT): a randomised controlled trial of intervention before the onset of type 1 diabetes. *Lancet* 2004; 363: 925-31.

4. Elam MB, *et al.* Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease: the ADMIT study: a randomized trial. *JAMA* 2000; 284: 1263-70.

5. Grundy SM, *et al.* Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidaemia associated with type 2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of Niaspan trial. *Arch Intern Med* 2002; 162: 1568-76.

Hyperlipidaemias. The first-line treatment for hyperlipidaemias remains dietary and lifestyle modification; where this fails, drug therapy may be considered (p.1287). Nicotinic acid is reported to have a favourable effect on blood-lipid profiles, raising high-density lipoprotein (HDL)-cholesterol and lowering low-density lipoprotein (LDL)-cholesterol.^{1,3} Nicotinic acid is used particularly in familial hypertriglyceridaemia, or in familial combined hyperlipidaemia when both triglyceride and cholesterol concentrations are similarly elevated. Nicotinic acid was less effective than lovastatin at reducing LDL-cholesterol in patients with primary hypercholesterolaemia, but more effective at increasing HDL-cholesterol; lovastatin was better tolerated.⁴ A combination of nicotinic acid with lovastatin was found to be comparable to atorvastatin and more effective than simvastatin in reducing LDL-cholesterol, and more effective than either atorvastatin or simvastatin in increasing HDL-cholesterol, in a study of patients with dyslipidaemia.⁵ Some have recommended that nicotinic acid be substituted for a statin to lower LDL-cholesterol when patients cannot tolerate a statin.⁶ Combination therapy is recommended when the reduction in LDL-cholesterol is insufficient with statin monotherapy,^{7,8} or when raising HDL-cholesterol would be beneficial,^{9,10} as in patients with type 2 diabetes mellitus, or the metabolic syndrome.⁸ The risk of muscle toxicity with this combination is not considered to be significantly different to that with statin monotherapy.¹⁰ A combination of nicotinic acid with laropirant has been developed in an attempt to reduce flushing;¹¹⁻¹³ it has also been used for combination therapy with a statin.¹⁴

1. McKenney JM, *et al.* A comparison of the efficacy and toxic effects of sustained- vs immediate-release niacin in hypercholesterolemic patients. *JAMA* 1994; 271: 672-7.

2. McKenney J. Niacin for dyslipidemia: considerations in product selection. *Am J Health-Syst Pharm* 2003; 60: 995-1005.

3. McCormack PL, Keating GM. Prolonged-release nicotinic acid: a review of its use in the treatment of dyslipidaemia. *Drugs* 2005; 65: 2719-40.

4. Illingworth DR, *et al.* Comparative effects of lovastatin and niacin in primary hypercholesterolemia: a prospective trial. *Arch Intern Med* 1994; 154: 1586-95.

5. Bays HE, *et al.* Comparison of once-daily, Niacin extended-release/lovastatin with standard doses of atorvastatin and simvastatin (The Advicor Versus Other Cholesterol-Modulating Agents Trial Evaluation [ADVOCATE]). *Am J Cardiol* 2003; 91: 667-72.

6. Miller M. Niacin as a component of combination therapy for dyslipidemia. *Mayo Clin Proc* 2003; 78: 735-42.

7. McKenney J. New perspectives on the use of niacin in the treatment of lipid disorders. *Arch Intern Med* 2004; 164: 697-705.

8. Chapman MJ, *et al.* Raising high-density lipoprotein cholesterol with reduction of cardiovascular risk: the role of nicotinic acid—a position paper developed by the European Consensus Panel on HDL-C. *Curr Med Res Opin* 2004; 20: 1253-68.

9. Yim BT, Chong PH. Niacin-ER and lovastatin treatment of hypercholesterolemia and mixed dyslipidemia. *Ann Pharmacother* 2003; 37: 106-15.

10. Robinson JG. Management of complex lipid abnormalities with a fixed dose combination of simvastatin and extended release niacin. *Vasc Health Risk Manag* 2009; 5: 31-43.

11. Perry CM. Extended-release niacin (nicotinic acid)/laropirant. *Drugs* 2009; 69: 1665-79.

12. Bays HE, Ballantyne C. What's the deal with niacin development: is laropirant add-on therapy a winning strategy to beat a straight flush? *Curr Opin Lipidol* 2009; 20: 467-76.

13. Parhofer KG. Review of extended-release niacin/laropirant fixed combination in the treatment of mixed dyslipidemia and primary hypercholesterolemia. *Vasc Health Risk Manag* 2009; 5: 901-8.

14. Yiu KH, *et al.* A new paradigm for managing dyslipidemia with combination therapy: laropirant + niacin + simvastatin. *Expert Opin Invest Drugs* 2010; 19: 437-49.

Pemphigus. Oral treatment with nicotinamide and a tetracycline¹⁻⁶ has controlled lesions in pemphigus and pemphigoid (p.1722), including persistent pemphigoid gestationis,⁵ and ocular cicatricial pemphigoid.⁶

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3. Reiche L, *et al.* Combination therapy with nicotinamide and tetracyclines for cicatricial pemphigoid: further support for its efficacy. *Clin Exp Dermatol* 1998; 23: 254-7.

4. Goon ATJ, *et al.* Tetracycline and nicotinamide for the treatment of bullous pemphigoid: our experience in Singapore. *Singapore Med J* 2000; 41: 327-30.

5. Amato L, *et al.* Successful treatment with doxycycline and nicotinamide of two cases of persistent pemphigoid gestationis. *J Dermatol Treat* 2002; 13: 143-6.

6. Dragan L, *et al.* Tetracycline and nicotinamide: treatment alternatives in ocular cicatricial pemphigoid. *Cutis* 1999; 63: 181-3.

Preparations

BP 2010: Nicotinamide Tablets; Nicotinic Acid Tablets; Vitamins B and C Injection;

BPC 1973: Compound Vitamin B Tablets; Strong Compound Vitamin B Tablets;

USP 33: Niacin Injection; Niacin Tablets; Nicotinamide Injection; Nicotinamide Tablets; Oil- and Water-soluble Vitamins Capsules; Oil- and Water-soluble Vitamins Oral Solution; Oil- and Water-soluble Vitamins Tablets; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Oil- and Water-soluble Vitamins with Minerals Tablets; Water-soluble Vitamins Capsules; Water-soluble Vitamins Tablets; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Proprietary Preparations (details are given in Volume B)

Arg: NB-3; Niaspan; Nicozinc; **Austral:** Papulex; **Austria:** Direktan; Niaspan; Nicovitol; **Belg:** Ucermine PP; **Braz:** Acinic; Pletri; Papulex; **Canada:** Niaspan; Nicot; **Chile:** Cotina; Niacet; Niaspan; Veridart; **Fin:** Niaspan; **Fr:** Niaspan; Nicobion; **Ger:** Niaspan; Nicobion; **Gr:** Nicovitol; **Hong Kong:** Niaspan; Nicocin; **India:** Nialip; **Indon:** Niacet; Niaspan; **Ir:** Niaspan; Nicam; Pelzont; **Mex:** Hipocot Nacro; Niaspan; Pevevit; **Neth:** Niaspan; **Norw:** Niaspan; **Philipp:** Niaspan; **Port:** Niaspan; **Rus:** Vita-Ioduro (Вита-Иодуrol); **Singapore:** Niaspan; Papulex Oil-free; **Swed:** Niaspan; Nicangin; **Switz:** Niaspan; **Thai:** Niaspan; Nicotab; **Turk:** Niascor; Niaspan; **UK:** Freederm; Niaspan; Nicam; **UKr:** Nicospas (Нікоспан); **USA:** Endur-acin; Niaspan; Slo-Niacin; **Venez:** Niaspan.

Multi-ingredient Arg: Anemidox; Atomo Ordenador; Centella Asiatica Compuesta; IP-6; Nicozinc; Proavonol Omeopatia; **Austral:** Chiblain Formula; Cirlo; Dynamio; Gingo A; Papulex; Prochol; Silybum Complex; Sensesent Anti Ageing Face; **Austria:** Diligan; Pertombont; Spasmocor; **Belg:** Thistalex; **Braz:** Frutoplex; Frutovene; Gabat; **Sadon:** Canad; **Advicor:** Formula 7441; Formula 7442; Inner Shade; Lipofactors & Niacin; Niacin; PML Crono; **Chile:** Becomplina Forte; Benutrex 1000; Nicapost; Efficar Al; Exomega; Kenum Anticapa Intensivo; Pefungol; Proavon; Rodepar; Ureadin Forte; Ureadin Rx FS; Ureadin Rx RD; **Cz:** Pelzont; Tredaptive; Trevalyn; Uppavit; **Fin:** Neurovitan; Vertipam; **Ir:** Liporegul; Suren; Tredaptive; TTD-B; **It:** Vita-Dermace; **Ger:** Eisekapseln; Eukalisan N; Floradix Kruterpilz; Petehaj; **Gr:** Collyre Vitaphakol; **Spain:** Tredaptive; Vertigo-Venex; **Hung:** Dietet-In; Klimin; Obesmin; **India:** Diligan; Genpro; Hepa-Merz; Kalzina; Livogen; Livosil-B; Neogadine SG; Neurophosphates; Neurotar; Nutrozyme; Sioneuron; **Indon:** Balin Q10; Biocholesil; Carni Plus; Ceretone; Complex; Dansera; Dialac; Hemaviton Jeng; Kitoles; Sangobion Active; Sotens; Tonikum Bay; **Vonin:** Yeastofort; **Ir:** Crampex; Efficar Al; Efficor; Quiet Life; Tredaptive; Trevalyn; **Israel:** Babyzin; **Ital:** Emorion; Epargisocet; Fisioreve CH; Fofoliga B12; Fosforilax; Konordim; Novostatin; Pinesal; PML Crono; Promelonin; Solvobit; Virman Plus; **Malaysia:** Dermahel DeAkin; **N:** Trovite; **Mon:** Monasent; Viturine; **NZ:** Tredaptive; **Philipp:** Hiruscar; Jeleparr; Tredaptive; **Pol:** Dermalin; **Port:** Cicapost; Diligan; Pelzont; Redusan Plus; Tredaptive; Trevalyn; Ureadin Forte; **Rus:** Cytolavin (Литофлавин); Doppelherz Ginseng Aktiv (Доппелгерци Женьшен Актив); Essilver Forte (Эссильвер Форте); Lidevin (Лидевин); Multi-Tabs B-Complex (Мульти-Табс В-Комплекс); Oftan Catichrom (Офтан Катахром); Ulenzyme с МРS (Улензим с МРS); **S Afr:** Cosaldon; **Singapore:** Beafort; Beaplex; Erase; Ferbeaplex; Papulex Isocorexion; PML Crono; **Spain:** Depurativo Richelet; Eufolofonia Vigor; Euzyma Lina; Ili; Euzyma Lina Ili; Vitaphakol; **Swed:** Theranil; **Thai:** B-100 Complex; **Turk:** Epargisocet; **UK:** Camplex; Efficor; Quiet Life; S.F.H.P; Tredaptive; Vitallux Plus; **UKr:** B-Complex Multi-Tabs (В-Комплекс Мульти-Табс); Cytolavin (Литофлавин); Decamvit (Декамевит); Fenules (Фенюльс); Hepaforte (Гепатофорте); Levasil (Левасил); Lidevin (Лидевин); Sedavit (Седавит); Vita-Ioduro (Вита-Иодуrol); **USA:** Advicor; Nicomide; Simcor; **Venez:** Tegat.

Homeopathic: **Austral:** Heer-More; **Ger:** Infi-China; Infi-Symptom; Infi-nepant.

Olafur (BAN, USAN, rINN)

Amine Fluoride 297; GA-297; Olafurum; SKF-38095, 2,2'-(3-[N-(2-Hydroxyethyl)octadecylamino]propylimino)diethanol dihydrofluoride.

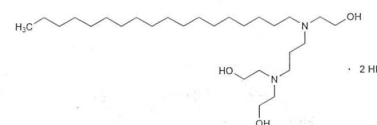
Олафлур

C₂₇H₅₀F₂N₂O₃ = 498.8.

CA₂ — 6818-37-7.

ATC — A01AA03.

ATC Vet — QA01AA03.



Profile

Olafur is used as a source of fluoride (see Sodium Fluoride, p.1223) in the prevention of dental caries. For a report of stoma-