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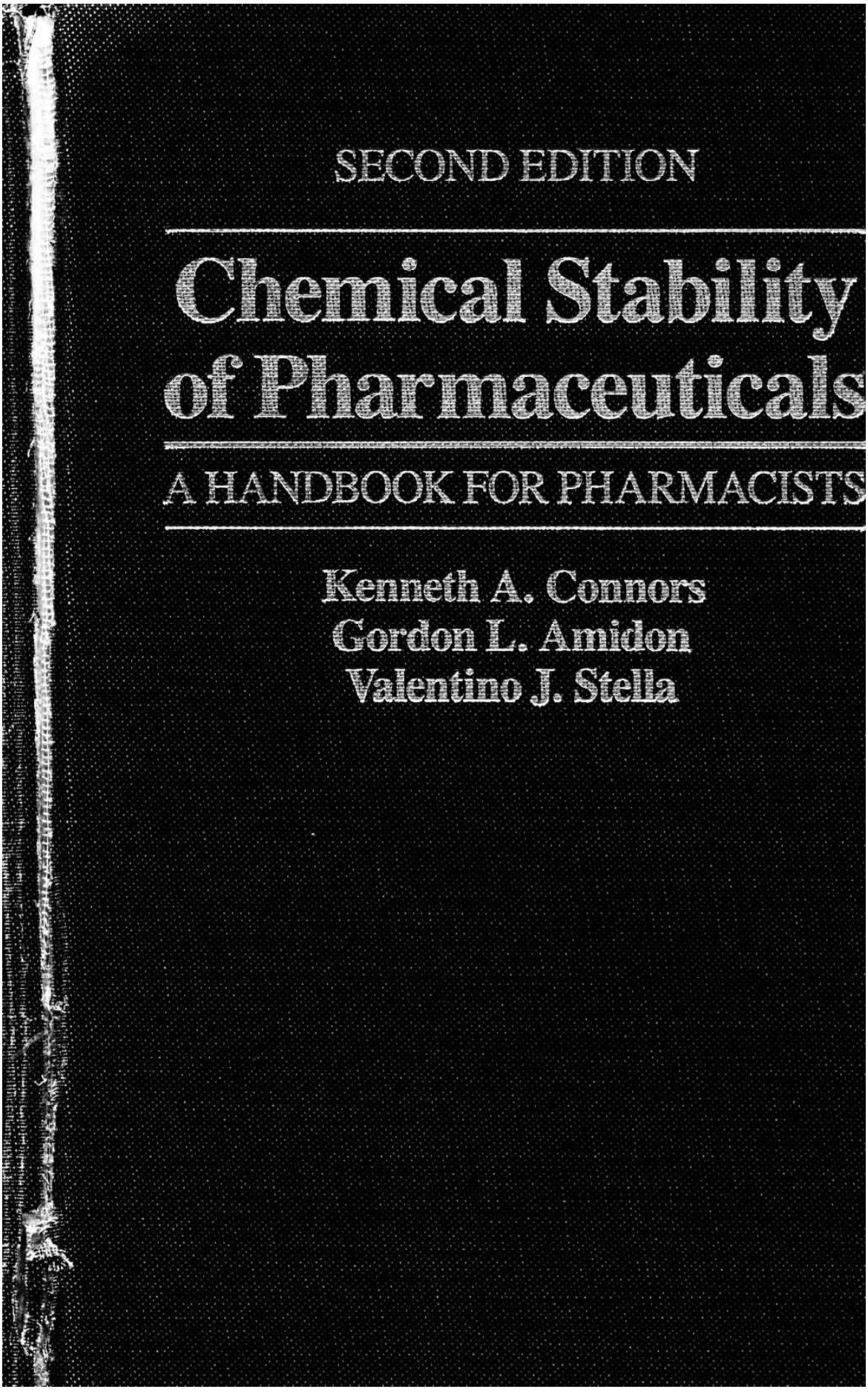
SECOND EDITION
Chemical Stability of Pharmaceuticals
A HANDBOOK FOR PHARMACISTS
Kenneth A. Connors
Gordon L. Amidon
Valentino J. Stella

Chemical Stability of Pharmaceuticals

Chemical Stability of Pharmaceuticals

A Handbook for Pharmacists

Second Edition

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School of Pharmacy, The University of Wisconsin

Gordon L. Amidon
College of Pharmacy, The University of Michigan

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A Wiley-Interscience Publication
JOHN WILEY & SONS
New York • Chichester • Brisbane • Toronto • Singapore

$55.00

Library of Congress Cataloging in Publication Data:

Connors, Kenneth A. (Kenneth Antonio), 1932–
Chemical stability of pharmaceuticals.

"A Wiley-Interscience publication."
Includes bibliographies and index.
1. Drug stability. I. Amidon, Gordon L. II. Stella, Valentino J., 1946– . III. Title. [DNLM: 1. Drug Stability—handbooks. 2. Kinetics—handbooks. QV 735 C752c]

RS424.C66 1986 615'.18 85-31455
ISBN 0-471-87955-X

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

To the memory of Lloyd Kennon

Contents

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Item policy	**general (book)**
Provenance	
Is magnetic	**No**
PO Line	Select from a list
Issue date	
Receiving date	**09/12/2012**
Expected receiving date	
Enumeration A	
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Date: December 14, 2018

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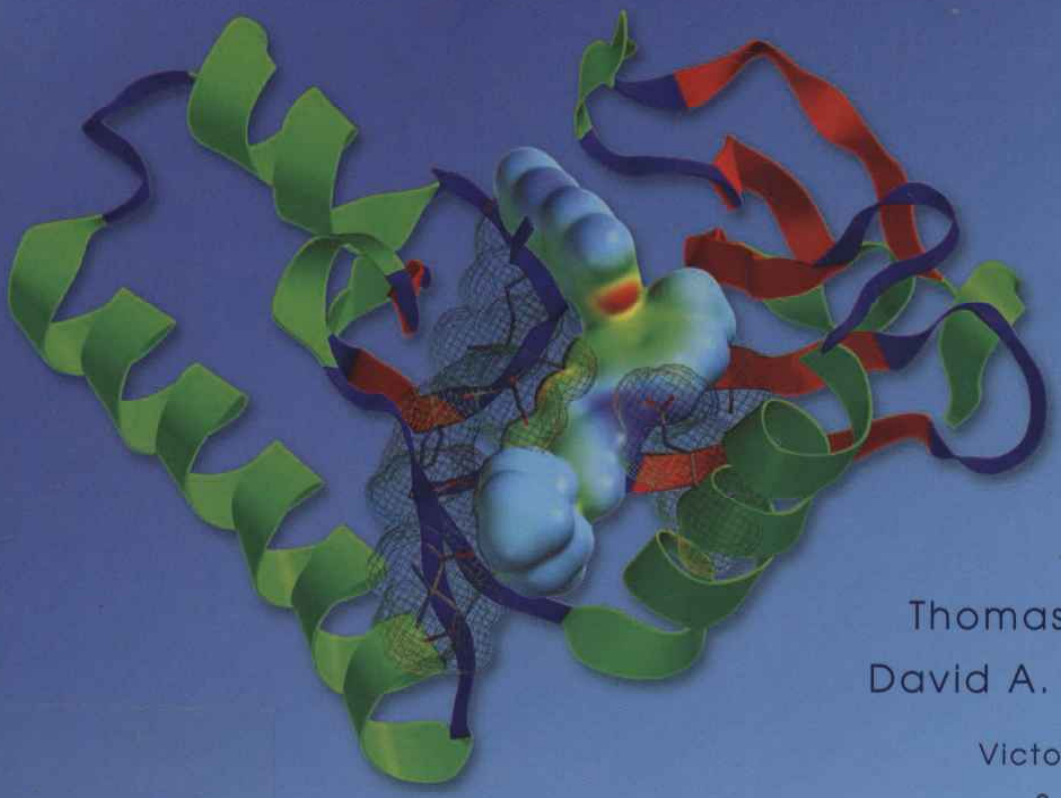
FOYE'S PRINCIPLES OF

MEDICINAL CHEMISTRY

SIXTH EDITION



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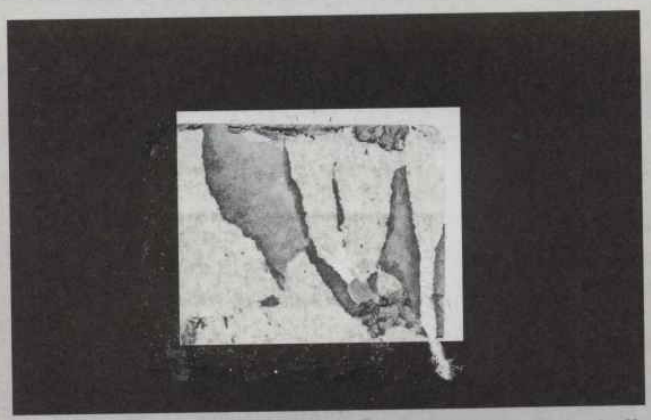

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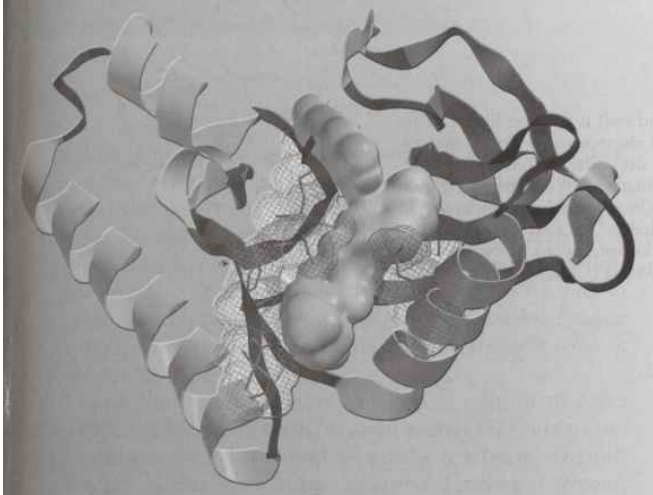

FOYE'S Principles of Medicinal Chemistry

SIXTH EDITION

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Sixth Edition

351 West Camden Street
Baltimore, MD 21201

530 Walnut Street
Philadelphia, PA 19106

Printed in the USA

9 8 7 6 5 4

Library of Congress Cataloging-in-Publication Data

Foye's principles of medicinal chemistry / edited by Thomas L. Lemke . . . [et al.]. — 6th ed.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-0-7817-6879-5
1. Pharmaceutical chemistry. I. Foye, William O. II. Lemke, Thomas L.
III. Title: Principles of medicinal chemistry.
[DNLM: 1. Chemistry, Pharmaceutical. QV 744 F7962 2008]
RS403.P75 2008
616.07'56—dc22

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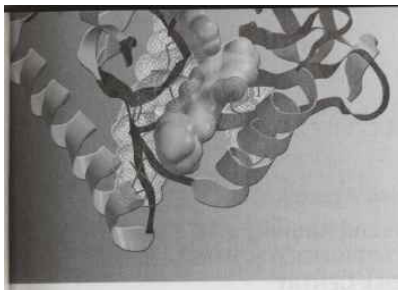
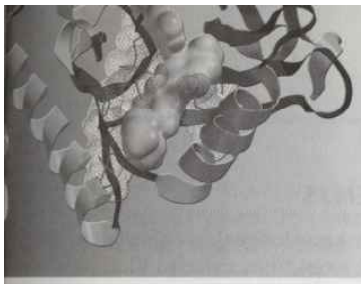


CONTENTS



PREFACE

As defined by IUPAC, medicinal chemistry is a chemistry-based discipline, involving aspects of biological, medical and pharmaceutical sciences. It is concerned with the invention, discovery, design, identification and preparation of biologically active compounds, the study of their metabolism, the interpretation of their mode of action at the molecular level and the construction of structure-activity relationships (SAR), the relationship between chemical structure and pharmacological activity for a series of compounds.

As we look back 33 years to the first edition of *Foye's Principles of Medicinal Chemistry* and nearly 60 years to the first edition of Wilson and Gisvold's textbook, *Organic Chemistry in Pharmacy* (later renamed *Textbook of Organic Medicinal and Pharmaceutical Chemistry*), we can examine how the teaching of medicinal chemistry has evolved over the last half of the 20th century. Fifty years ago the approach to teaching drug classification was based on chemical functional groups; in the 1970s it was the relationship between chemical structure and pharmacological activity for a series of compounds, and today it is the integration of these principles with pharmacology and therapeutics into a single multi-semester course called pharmacodynamics, pharmacotherapeutics, or another similar name. Drug discovery and development maintains its role in traditional drug therapy, but its application to pharmacogenomics may well become the treatment modality of the future. The scope of knowledge in organic chemistry, biochemistry, pharmacology, and therapeutics allows students to make generalizations connecting the physicochemical properties of small organic molecules and peptides to the receptor and biochemical properties of living systems. As a consequence, these generalizations, validated by repetitive examples, emerge in time as principles of drug discovery and drug mechanisms, principles that describe the structural relationships between diverse organic molecules and the biomolecular functions that predict their mechanisms toward controlling diseases.

Medicinal chemistry is central to modern drug discovery and development. For most of the 20th century, the majority of drugs were discovered either by identifying the active ingredient in traditional natural remedies, by rational drug design, or by serendipity. Medicinal chemistry has advanced during the past several decades from not only synthesizing new compounds but to understanding the molecular basis of a disease and its control, identifying biomolecular targets implicated as disease-causing, and ultimately inventing specific compounds (called "hits") that block the biomolecules from progressing to an illness or stop the disease in its tracks. Medicinal chemists use structure-activity relationships to improve the "hits" into "lead candidates" by optimizing their selectivity against the target and reducing their activity against nontargets, and ADME (pharmacokinetics) to understand how the body causes drug clearance, what's involved in drug distribution, and the nature of the molecules that control those factors.

We are both medicinal chemists, and our approaches to editing this sixth edition of *Foye's Principles of Medicinal Chemistry* are influenced by our respective academic backgrounds. We believe that our collaboration on this textbook represents a melding of our perspectives that will provide new dimensions of appreciation and understanding for all students. In editing this multi-authored book we have tried to ensure a more-or-less consistent style in the organization of the respective chapters.

ORGANIZATIONAL PHILOSOPHY

The organizational approach we take in this textbook builds from the principles of drug discovery, physicochemical properties of drug molecules, and ADMET (absorption-distribution-metabolism-excretion-toxicity) to their integration into therapeutic substances. Our challenge has been to provide a comprehensive description of drug discovery and pharmacodynamic agents in an introductory textbook. To address the increasing emphasis in U.S. pharmacy schools to integrating medicinal chemistry with pharmacology and clinical pharmacy and the creation of one-semester principle courses, we organized the book into four parts: Part I: Principles of Drug Discovery; Part II: Drug Receptors Affecting Neurotransmission and Enzymes as Catalytic Receptors; Part III: Pharmacodynamic Agents (with further subdivision into drugs affecting different systems of the body); and Part IV: Disease State Management. Parts I and II are designed for the one-semester course in principles of drug discovery and Parts II through IV for an integrated course or courses in pharmacodynamics/pharmacotherapeutics.

WHAT IS NEW IN THIS EDITION

The pharmacist sits at the interphase between the healthcare system and the patient. The pharmacist has the responsibility for improving the quality of life of the patient by assuring the appropriate use of pharmaceuticals. To do this appropriately, the pharmacist must bring together the basic sciences of chemistry, biology, biopharmaceutics and pharmacology with the clinical sciences. In an attempt to relate the importance of medicinal

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Material type	**Book**
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Is magnetic	**No**
PO Line	Select from a list
Issue date	
Receiving date	**04/13/2011**
Expected receiving date	
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Enumeration B	

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Date: February 14, 2019

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Handbook of Pharmaceutical Excipients

SIXTH EDITION

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London • Chicago
Pharmaceutical Press

Published by the Pharmaceutical Press
An imprint of RPS Publishing

1 Lambeth High Street, London SE1 7JN, UK
100 South Atkinson Road, Suite 200, Grayslake, IL 60030-7820, USA

and the American Pharmacists Association
2215 Constitution Avenue, NW, Washington, DC 20037-2985, USA

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

First published 1986
Second edition published 1994
Third edition published 2000
Fourth edition published 2003
Fifth edition published 2006
Sixth edition published 2009

Typeset by Data Standards Ltd, Frome, Somerset
Printed in Italy by L.E.G.O. S.p.A.

ISBN 978 0 85369 792 3 (UK)
ISBN 978 1 58212 135 2 (USA)

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

Benzalkonium Chloride

B

1 Nonproprietary Names

BP: Benzalkonium Chloride

JP: Benzalkonium Chloride

PhEur: Benzalkonium Chloride

USP-NF: Benzalkonium Chloride

2 Synonyms

Alkylbenzyldimethylammonium chloride; alkyl dimethyl benzyl ammonium chloride; benzalkonii chloridum; BKC; *Hyamine 3500*; *Pentonium*; *Zephiran*.

3 Chemical Name and CAS Registry Number

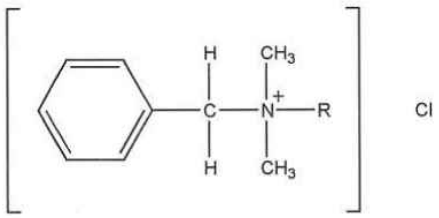
Alkyldimethyl(phenylmethyl)ammonium chloride [8001-54-5]

4 Empirical Formula and Molecular Weight

The USP32–NF27 describes benzalkonium chloride as a mixture of alkylbenzyldimethylammonium chlorides of the general formula $[C_6H_5CH_2N(CH_3)_2R]Cl$, where R represents a mixture of alkyls, including all or some of the group beginning with *n*-C_8H_{17} and extending through higher homologs, with *n*-$C_{12}H_{25}$, *n*-$C_{14}H_{29}$, and *n*-$C_{16}H_{33}$ comprising the major portion.

The average molecular weight of benzalkonium chloride is 360.

5 Structural Formula



R = mixture of alkyls: *n*-C_8H_{17} to *n*-$C_{18}H_{37}$; mainly *n*-$C_{12}H_{25}$ (dodecyl), *n*-$C_{14}H_{29}$ (tetradecyl), and *n*-$C_{16}H_{33}$ (hexadecyl).

6 Functional Category

Antimicrobial preservative; antiseptic; disinfectant; solubilizing agent; wetting agent.

7 Applications in Pharmaceutical Formulation or Technology

Benzalkonium chloride is a quaternary ammonium compound used in pharmaceutical formulations as an antimicrobial preservative in applications similar to other cationic surfactants, such as cetrimide.

In ophthalmic preparations, benzalkonium chloride is one of the most widely used preservatives,[1] at a concentration of 0.01–0.02% w/v. Often it is used in combination with other preservatives or excipients, particularly 0.1% w/v disodium edetate, to enhance its antimicrobial activity against strains of *Pseudomonas*.

In nasal,[2] and otic formulations a concentration of 0.002–0.02% w/v is used, sometimes in combination with 0.002–0.005% w/v thimerosal. Benzalkonium chloride 0.01% w/v is also employed as a preservative in small-volume parenteral products. Benzalkonium chloride was also shown to enhance the topical penetration of lorazepam.[3]

Benzalkonium chloride is additionally used as a preservative in cosmetics.

8 Description

Benzalkonium chloride occurs as a white or yellowish-white amorphous powder, a thick gel, or gelatinous flakes. It is hygroscopic, soapy to the touch, and has a mild aromatic odor and very bitter taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for benzalkonium chloride.

Test	JP XV	PhEur 6.4	USP32–NF27
Identification	+	+	+
Characters	+	+	–
Acidity or alkalinity	–	+	–
Appearance of solution	+	+	–
Water	≤15.0%	≤10.0%	≤15.0%
Residue on ignition	≤0.2%	–	≤2.0%
Sulfated ash	–	≤0.1%	–
Water-insoluble matter	–	–	+
Foreign amines	–	+	+
Ratio of alkyl components	–	+	+
Petroleum ether-soluble substances	≤1.0%	–	–
Benzyl alcohol	–	≤0.5%	–
Benzaldehyde	–	≤0.15%	–
Chloromethylbenzene	–	≤0.05%	–
Assay (dried basis)			
of *n*-$C_{12}H_{25}$	–	–	≥40.0%
of *n*-$C_{14}H_{29}$	–	–	≥20.0%
of *n*-$C_{12}H_{25}$ and *n*-$C_{14}H_{29}$	–	–	≥70.0%
for total alkyl content	95.0–105.0%	95.0–104.0%	97.0–103.0%

10 Typical Properties

Acidity/alkalinity pH = 5–8 for a 10% w/v aqueous solution.

Antimicrobial activity Benzalkonium chloride solutions are active against a wide range of bacteria, yeasts, and fungi. Activity is more marked against Gram-positive than Gram-negative bacteria and minimal against bacterial endospores and acid-fast bacteria, *see* Table II. The antimicrobial activity of benzalkonium chloride is significantly dependent upon the alkyl composition of the homolog mixture.[4] Benzalkonium chloride is ineffective against some *Pseudomonas aeruginosa* strains, *Mycobacterium tuberculosis*, *Trichophyton interdigitale*, and *T. rubrum*. However, combined with disodium edetate (0.01–0.1% w/v), benzyl alcohol, phenylethanol, or phenylpropanol, the activity against *Pseudomonas aeruginosa* is increased.[5] Antimicrobial activity may also be enhanced by the addition of phenylmercuric acetate, phenylmercuric borate, chlorhexidine, cetrimide, or *m*-cresol.[6,7] In the presence of citrate and phosphate buffers (but not borate), activity against *Pseudomonas* can be reduced. *See also* Sections 11 and 12. Benzalkonium chloride is relatively inactive against spores and molds, but is active against some viruses, including HIV.[8] Inhibitory activity

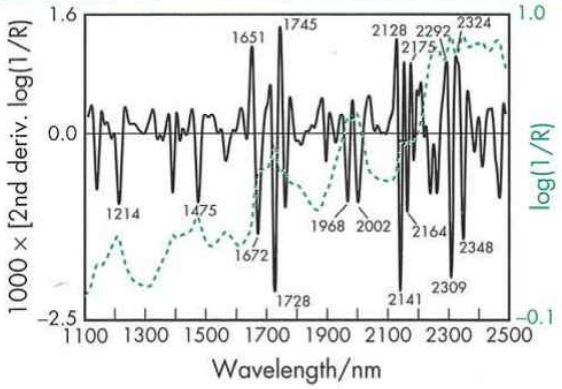


Figure 1: Near-infrared spectrum of benzalkonium chloride measured by reflectance.

increases with pH, although antimicrobial activity occurs at pH 4–10.

Table II: Minimum inhibitory concentrations (MICs) of benzalkonium chloride.

Microorganism	MIC (μg/mL)
Aerobacter aerogenes	64
Clostridium histolyticum	5
Clostridium oedematiens	5
Clostridium tetani	5
Clostridium welchii	5
Escherichia coli	16
Pneumococcus II	5
Proteus vulgaris	64
Pseudomonas aeruginosa	30
Salmonella enteritidis	30
Salmonella paratyphi	16
Salmonella typhosa	4
Shigella dysenteriae	2
Staphylococcus aureus	1.25
Streptococcus pyrogenes	1.25
Vibrio cholerae	2

Density ≈0.98 g/cm^3 at 20°C
Melting point ≈40°C
NIR spectra *see* Figure 1.
Partition coefficients The octanol : water partition coefficient varies with the alkyl chain length of the homolog: 9.98 for C_{12}, 32.9 for C_{14}, and 82.5 for C_{16}.
Solubility Practically insoluble in ether; very soluble in acetone, ethanol (95%), methanol, propanol, and water. Aqueous solutions of benzalkonium chloride foam when shaken, have a low surface tension and possess detergent and emulsifying properties.

11 Stability and Storage Conditions

Benzalkonium chloride is hygroscopic and may be affected by light, air, and metals.

Solutions are stable over a wide pH and temperature range and may be sterilized by autoclaving without loss of effectiveness. Solutions may be stored for prolonged periods at room temperature. Dilute solutions stored in polyvinyl chloride or polyurethane foam containers may lose antimicrobial activity.

The bulk material should be stored in an airtight container, protected from light and contact with metals, in a cool, dry place.

12 Incompatibilities

Incompatible with aluminum, anionic surfactants, citrates, cotton, fluorescein, hydrogen peroxide, hypromellose,[9] iodides, kaolin, lanolin, nitrates, nonionic surfactants in high concentration, permanganates, protein, salicylates, silver salts, soaps, sulfonamides, tartrates, zinc oxide, zinc sulfate, some rubber mixes, and some plastic mixes.

Benzalkonium chloride has been shown to be adsorbed to various filtering membranes, especially those that are hydrophobic or anionic.[10]

13 Method of Manufacture

Benzalkonium chloride is formed by the reaction of a solution of *N*-alkyl-*N*-methylbenzamine with methyl chloride in an organic solvent suitable for precipitating the quaternary compound as it is formed.

14 Safety

Benzalkonium chloride is usually nonirritating, nonsensitizing, and is well tolerated in the dilutions normally employed on the skin and mucous membranes. However, benzalkonium chloride has been associated with adverse effects when used in some pharmaceutical formulations.[11]

Ototoxicity can occur when benzalkonium chloride is applied to the ear[12] and prolonged contact with the skin can occasionally cause irritation and hypersensitivity. Benzalkonium chloride is also known to cause bronchoconstriction in some asthmatics when used in nebulizer solutions.[13–17]

Toxicity experiments with rabbits have shown benzalkonium chloride to be harmful to the eye in concentrations higher than that normally used as a preservative. However, the human eye appears to be less affected than the rabbit eye and many ophthalmic products have been formulated with benzalkonium chloride 0.01% w/v as the preservative.

Benzalkonium chloride is not suitable for use as a preservative in solutions used for storing and washing hydrophilic soft contact lenses, as the benzalkonium chloride can bind to the lenses and may later produce ocular toxicity when the lenses are worn.[18] Solutions stronger than 0.03% w/v concentration entering the eye require prompt medical attention.

Local irritation of the throat, esophagus, stomach, and intestine can occur following contact with strong solutions (>0.1% w/v). The fatal oral dose of benzalkonium chloride in humans is estimated to be 1–3 g. Adverse effects following oral ingestion include vomiting, collapse, and coma. Toxic doses lead to paralysis of the respiratory muscles, dyspnea, and cyanosis.

LD_{50} (mouse, oral): 150 mg/kg[19]
LD_{50} (rat, IP): 14.5 mg/kg
LD_{50} (rat, IV): 13.9 mg/kg
LD_{50} (rat, oral): 300 mg/kg
LD_{50} (rat, skin): 1.42 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Benzalkonium chloride is irritant to the skin and eyes and repeated exposure to the skin may cause hypersensitivity. Concentrated benzalkonium chloride solutions accidentally spilled on the skin may produce corrosive skin lesions with deep necrosis and scarring, and should be washed immediately with water, followed by soap solutions applied freely. Gloves, eye protection, and suitable protective clothing should be worn.

16 Regulatory Status

Included in the FDA Inactive Ingredients Database (inhalations, IM injections, nasal, ophthalmic, otic, and topical preparations).

Included in nonparenteral medicines licensed in the UK. It is also included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Benzethonium chloride; cetrimide.

18 Comments

Benzalkonium chloride has been used in antiseptic wipes and has been shown to produce significantly less stinging or burning than isopropyl alcohol and hydrogen peroxide.[20]

The EINECS numbers for benzalkonium chloride are 264-151-6; 260-080-8; 269-919-4; 270-325-2; 287-089-1. The PubChem Compound ID (CID) for benzalkonium chloride is 3014024

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21 Author

AH Kibbe.

22 Date of Revision

15 January 2009.

Benzethonium Chloride

1 Nonproprietary Names

BP: Benzethonium Chloride
JP: Benzethonium Chloride
PhEur: Benzethonium Chloride
USP: Benzethonium Chloride

2 Synonyms

Benzethonii chloridum; benzyldimethyl-[2-[2-(*p*-1,1,3,3-tetramethylbutylphenoxy) ethoxy]ethyl]ammonium chloride; BZT; diisobutylphenoxyethoxyethyl dimethyl benzyl ammonium chloride; *Hyamine 1622*.

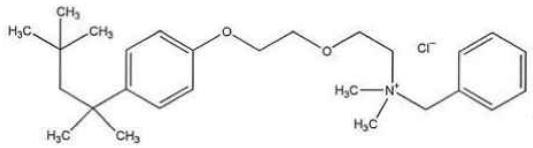
3 Chemical Name and CAS Registry Number

N,*N*-Dimethyl-*N*-[2-[2-[4-(1,1,3,3-tetramethylbutyl)phenoxy]ethoxy]ethyl]benzene-methanaminium chloride [121-54-0]

4 Empirical Formula and Molecular Weight

$C_{27}H_{42}ClNO_2$ 448.10

5 Structural Formula



6 Functional Category

Antimicrobial preservative; antiseptic; disinfectant.

7 Applications in Pharmaceutical Formulation or Technology

Benzethonium chloride is a quaternary ammonium compound used in pharmaceutical formulations as an antimicrobial preservative. Typically, it is used for this purpose in injections, ophthalmic and otic preparations at concentrations 0.01–0.02% w/v. Benzethonium chloride may also be used as a wetting and solubilizing agent, and as a topical disinfectant.[1,2]

In cosmetics such as deodorants, benzethonium chloride may be used as an antimicrobial preservative in concentrations up to 0.5% w/v.

The physical properties and applications of benzethonium chloride are similar to those of other cationic surfactants such as cetrimide.

8 Description

Benzethonium chloride occurs as a white crystalline material with a mild odor and very bitter taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for benzethonium chloride.

Test	JP XV	PhEur 6.0	USP 32
Identification	+	+	+
Characters	–	+	–
Appearance of solution	–	+	–
Acidity or alkalinity	–	+	–
Melting range	158–164°C	158–164°C	158–163°C
Loss on drying	≤5.0%	≤5.0%	≤5.0%
Residue on ignition	≤0.1%	–	≤0.1%
Sulfated ash	–	≤0.1%	–
Ammonium compounds	+	≤50 ppm	+
Assay (dried basis)	≥97.0%	97.0–103.0%	97.0–103.0%

10 Typical Properties

Acidity/alkalinity pH = 4.8–5.5 for a 1% w/v aqueous solution.

Antimicrobial activity Optimum antimicrobial activity occurs between pH 4–10. Preservative efficacy is enhanced by ethanol and reduced by soaps and other anionic surfactants. For typical minimum inhibitory concentrations (MICs) *see* Table II.[3]

Table II: Minimum inhibitory concentration (MIC) for benzethonium chloride.

Microorganism	MIC (μg/mL)
Aspergillus niger	128
Candida albicans	64
Escherichia coli	32
Penicillium notatum	64
Proteus vulgaris	64
Pseudomonas aeruginosa	250
Pseudomonas cepacia	250
Pseudomonas fluorescens	250
Staphylococcus aureus	0.5
Streptococcus pyogenes	0.5

NIR spectra *see* Figure 1.

Solubility Soluble 1 in less than 1 of acetone, chloroform, ethanol (95%), and water; soluble 1 in 6000 of ether. Dissolves in water to produce a foamy, soapy solution.

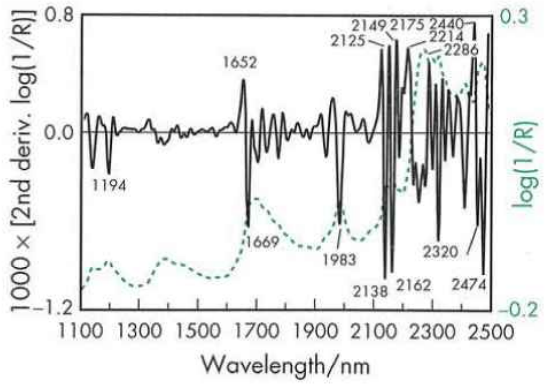


Figure 1: Near-infrared spectrum of benzethonium chloride measured by reflectance.

B

11 Stability and Storage Conditions

Benzethonium chloride is stable. Aqueous solutions may be sterilized by autoclaving.

The bulk material should be stored in an airtight container protected from light, in a cool, dry place.

12 Incompatibilities

Benzethonium chloride is incompatible with soaps and other anionic surfactants and may be precipitated from solutions greater than 2% w/v concentration by the addition of mineral acids and some salt solutions.

13 Method of Manufacture

p-Diisobutylphenol is condensed in the presence of a basic catalyst with β,β′-dichlorodiethyl ether to yield 2-[2-[4-(1,1,3,3-tetramethylbutyl)phenoxy]ethoxy]ethyl chloride. Alkaline dimethylamination then produces the corresponding tertiary amine which, after purification by distillation, is dissolved in a suitable organic solvent and treated with benzyl chloride to precipitate benzethonium chloride.[4]

14 Safety

Benzethonium chloride is readily absorbed and is generally regarded as a toxic substance when administered orally. Ingestion may cause vomiting, collapse, convulsions, and coma. The probable lethal human oral dose is estimated to be 50–500 mg/kg bodyweight.

The topical use of solutions containing greater than 5% w/v benzethonium chloride can cause irritation although benzethonium chloride is not regarded as a sensitizer. The use of 0.5% w/v benzethonium chloride in cosmetics is associated with few adverse effects. A maximum concentration of 0.02% w/v benzethonium chloride is recommended for use in cosmetics used in the eye area and this is also the maximum concentration generally used in pharmaceutical formulations such as injections and ophthalmic preparations.[5]

See also Benzalkonium Chloride.

LD_{50} (mouse, IP): 15.5 mg/kg[6]
LD_{50} (mouse, IV): 30 mg/kg
LD_{50} (mouse, oral): 338 mg/kg
LD_{50} (rat, IP): 16.5 mg/kg
LD_{50} (rat, IV): 19 mg/kg
LD_{50} (rat, oral): 368 mg/kg
LD_{50} (rat, SC): 119 mg/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Database (IM and IV injections; nasal, ophthalmic and otic preparations). Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Benzalkonium chloride; cetrimide.

18 Comments

Benzethonium chloride has been used therapeutically as a disinfectant and topical anti-infective agent. However, its use in these applications has largely been superseded by other more effective antimicrobials and it is now largely used solely as a preservative in a limited number of pharmaceutical and cosmetic formulations.

The EINECS number for benzethonium chloride is 204-479-9. The PubChem Compound ID (CID) for benethonium chloride includes 8478 and 547429.

19 Specific References

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21 Author

ME Quinn.

22 Date of Revision

27 January 2009.

Benzyl Alcohol

B

1 Nonproprietary Names

BP: Benzyl Alcohol
JP: Benzyl Alcohol
PhEur: Benzyl Alcohol
USP-NF: Benzyl Alcohol

2 Synonyms

Alcohol benzylicus; benzenemethanol; α-hydroxytoluene; phenylcarbinol; phenylmethanol; α-toluenol.

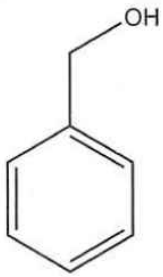
3 Chemical Name and CAS Registry Number

Benzenemethanol [100-51-6]

4 Empirical Formula and Molecular Weight

C_7H_8O 108.14

5 Structural Formula



6 Functional Category

Antimicrobial preservative; disinfectant; solvent.

7 Applications in Pharmaceutical Formulation or Technology

Benzyl alcohol is an antimicrobial preservative used in cosmetics, foods, and a wide range of pharmaceutical formulations,[1–4] including oral and parenteral preparations, at concentrations up to 2.0% v/v. The typical concentration used is 1% v/v, and it has been reported to be used in protein, peptide and small molecule products, although its frequency of use has fallen from 48 products in 1996, 30 products in 2001, to 15 products in 2006.[5] In cosmetics, concentrations up to 3.0% v/v may be used as a preservative. Concentrations of 5% v/v or more are employed as a solubilizer, while a 10% v/v solution is used as a disinfectant.

Benzyl alcohol 10% v/v solutions also have some local anesthetic properties, which are exploited in some parenterals, cough products, ophthalmic solutions, ointments, and dermatological aerosol sprays.

Although widely used as an antimicrobial preservative, benzyl alcohol has been associated with some fatal adverse reactions when administered to neonates. It is now recommended that parenteral products preserved with benzyl alcohol, or other antimicrobial preservatives, should not be used in newborn infants if at all possible; *see* Section 14.

8 Description

A clear, colorless, oily liquid with a faint aromatic odor and a sharp, burning taste.

9 Pharmacopeial Specifications

See Table I. *See also* Section 18.

Table I: Pharmacopeial specifications for benzyl alcohol.

Test	JP XV	PhEur 6.5	USP32–NF27
Identification	+	+	+
Characters	+	+	–
Solubility	+	+	–
Acidity	+	+	+
Clarity and color of solution	+	+	+
Specific gravity	1.043–1.049	1.043–1.049	–
Refractive index	1.538–1.541	1.538–1.541	1.538–1.541
Residue on evaporation	⩽0.05%	⩽0.05%	⩽0.05%
Related substances	+	+	+
Benzaldehyde	+	+	0.05–0.15
Peroxide value	⩽5	⩽5	⩽5
Assay	98.0–100.5%	98.0–100.5%	98.0–100.5%

10 Typical Properties

Acidity/alkalinity Aqueous solutions are neutral to litmus.

Antimicrobial activity Benzyl alcohol is bacteriostatic and is used as an antimicrobial preservative against Gram-positive bacteria, molds, fungi, and yeasts, although it possesses only modest bactericidal properties. Optimum activity occurs at pH below 5; little activity is shown above pH 8. Antimicrobial activity is reduced in the presence of nonionic surfactants, such as polysorbate 80. However, the reduction in activity is less than is the case with either hydroxybenzoate esters or quaternary ammonium compounds. The activity of benzyl alcohol may also be reduced by incompatibilities with some packaging materials, particularly polyethylene; *see* Section 12.

See Table II for reported minimum inhibitory concentrations (MICs).

Table II: Minimum inhibitory concentrations (MICs) of benzyl alcohol.[4]

Microorganism	MIC (μg/mL)
Aspergillus niger	5000
Candida albicans	2500
Escherichia coli	2000
Pseudomonas aeruginosa	2000
Staphylococcus aureus	25

Bacteria Benzyl alcohol is moderately active against most Gram-positive organisms (typical MICs are 3–5 mg/mL), although some Gram-positive bacteria are very sensitive (MICs 0.025–0.05 mg/mL). In general, benzyl alcohol is less active against Gram-negative organisms.

Fungi Benzyl alcohol is effective against molds and yeasts; typical MICs are 3–5 mg/mL.

Spores Benzyl alcohol is inactive against spores, but activity may be enhanced by heating. Benzyl alcohol 1% v/v, at pH 5–6, has been claimed to be as effective as phenylmercuric nitrate 0.002% w/v against *Bacillus stearothermophilus* at 100°C for 30 min.

Autoignition temperature 436.5°C
Boiling point 204.7°C
Flammability Flammable. Limits in air 1.7–15.0% v/v.
Flash point
100.6°C (closed cup);
104.5°C (open cup).
Freezing point −15°C
Partition coefficients
Liquid paraffin : water = 0.2;
Octanol : water = 1.10;
Peanut oil : water = 1.3.
Solubility *see* Table III.

Table III: Solubility of benzyl alcohol.

Solvent	Solubility at 20°C unless otherwise stated
Chloroform	Miscible in all proportions
Ethanol	Miscible in all proportions
Ethanol (50%)	1 in 1.5
Ether	Miscible in all proportions
Fixed and volatile oils	Miscible in all proportions
Water	1 in 25 at 25°C 1 in 14 at 90°C

Surface tension 38.8 mN/m (38.8 dynes/cm)
Vapor density (relative) 3.72 (air = 1)
Vapor pressure
13.3 Pa (0.1 mmHg) at 30°C;
1.769 kPa (13.3 mmHg) at 100°C.
Viscosity (dynamic) 6 mPa s (6 cP) at 20°C

11 Stability and Storage Conditions

Benzyl alcohol oxidizes slowly in air to benzaldehyde and benzoic acid; it does not react with water. Aqueous solutions may be sterilized by filtration or autoclaving; some solutions may generate benzaldehyde during autoclaving.

Benzyl alcohol may be stored in metal or glass containers. Plastic containers should not be used; exceptions to this include polypropylene containers or vessels coated with inert fluorinated polymers such as Teflon; *see* Section 12.

Benzyl alcohol should be stored in an airtight container, protected from light, in a cool, dry place.

12 Incompatibilities

Benzyl alcohol is incompatible with oxidizing agents and strong acids. It can also accelerate the autoxidation of fats.

Although antimicrobial activity is reduced in the presence of nonionic surfactants, such as polysorbate 80, the reduction is less than is the case with hydroxybenzoate esters or quaternary ammonium compounds.

Benzyl alcohol is incompatible with methylcellulose and is only slowly sorbed by closures composed of natural rubber, neoprene, and butyl rubber closures, the resistance of which can be enhanced by coating with fluorinated polymers.[6] However, a 2% v/v aqueous solution in a polyethylene container, stored at 20°C, may lose up to 15% of its benzyl alcohol content in 13 weeks.[7] Losses to polyvinyl chloride and polypropylene containers under similar conditions are usually negligible. Benzyl alcohol can damage polystyrene syringes by extracting some soluble components.[8]

13 Method of Manufacture

Benzyl alcohol is prepared commercially by the distillation of benzyl chloride with potassium or sodium carbonate. It may also be prepared by the Cannizzaro reaction of benzaldehyde and potassium hydroxide.

14 Safety

Benzyl alcohol is used in a wide variety of pharmaceutical formulations. It is metabolized to benzoic acid, which is further metabolized in the liver by conjugation with glycine to form hippuric acid, which is excreted in the urine.

Ingestion or inhalation of benzyl alcohol may cause headache, vertigo, nausea, vomiting, and diarrhea. Overexposure may result in CNS depression and respiratory failure. However, the concentrations of benzyl alcohol normally employed as a preservative are not associated with such adverse effects.

Reports of adverse reactions to benzyl alcohol[9,10] used as an excipient include toxicity following intravenous administration;[11–13] neurotoxicity in patients administered benzyl alcohol in intrathecal preparations;[14,15] hypersensitivity,[16–18] although relatively rare; and a fatal toxic syndrome in premature infants.[19–22]

The fatal toxic syndrome in low-birth-weight neonates, which includes symptoms of metabolic acidosis and respiratory depression, was attributed to the use of benzyl alcohol as a preservative in solutions used to flush umbilical catheters. As a result of this, the FDA has recommended that benzyl alcohol should not be used in such flushing solutions and has advised against the use of medicines containing preservatives in the newborn.[23,24]

The WHO has set the estimated acceptable daily intake of the benzyl/benzoic moiety at up to 5 mg/kg body-weight daily.[25]

LD_{50} (mouse, IV): 0.32 g/kg[26]
LD_{50} (mouse, oral): 1.36 g/kg
LD_{50} (rat, IP): 0.4 g/kg
LD_{50} (rat, IV): 0.05 g/kg
LD_{50} (rat, oral): 1.23 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Benzyl alcohol (liquid and vapor) is irritant to the skin, eyes, and mucous membranes. Eye protection, gloves, and protective clothing are recommended. Benzyl alcohol should be handled in a well-ventilated environment; a self-contained breathing apparatus is recommended in areas of poor ventilation. Benzyl alcohol is flammable.

16 Regulatory Status

Included in the FDA Inactive Ingredients Database (dental injections, oral capsules, solutions and tablets, topical, and vaginal preparations). Included in parenteral and nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

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18 Comments

Benzyl alcohol is one of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter <1196> in the USP32–NF27, the General Chapter 5.8 in PhEur 6.0, along with the 'State of Work' document on the PhEur EDQM website, and also the General Information Chapter 8 in the JP XV.

The EINECS number for benzyl alcohol is 202-859-9. The PubChem Compound ID (CID) for benzyl alcohol is 244.

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21 Author

RA Storey.

22 Date of Revision

3 February 2009.

Benzyl Benzoate

1 Nonproprietary Names

BP: Benzyl Benzoate
JP: Benzyl Benzoate
PhEur: Benzyl Benzoate
USP: Benzyl Benzoate

2 Synonyms

Benzoic acid benzyl ester; benzylbenzenecarboxylate; benzylis benzoas; benzyl phenylformate; phenylmethyl benzoate.

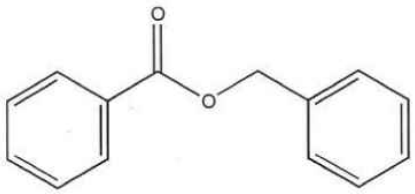
3 Chemical Name and CAS Registry Number

Benzoic acid phenylmethyl ester [120-51-4]

4 Empirical Formula and Molecular Weight

$C_{14}H_{12}O_2$ 212.24

5 Structural Formula



B

Table I: FCC specification for butylene glycol.[13]

Test	FCC 6
Distillation range	200–215°C
Lead	≤2 mg/kg
Specific gravity	1.004–1.006 at 20°C
Assay	≥99.0%

19 Specific References

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21 Authors

ME Quinn, RC Rowe.

22 Date of Revision

27 February 2009.

Butylparaben

1 Nonproprietary Names

BP: Butyl Hydroxybenzoate
JP: Butyl Parahydroxybenzoate
PhEur: Butyl Parahydroxybenzoate
USP-NF: Butylparaben

2 Synonyms

Butylis parahydroxybenzoas; butyl *p*-hydroxybenzoate; *CoSept B*; 4-hydroxybenzoic acid butyl ester; *Lexgard B*; *Nipabutyl*; *Tegosept B*; *Trisept B*; *Uniphen P-23*; *Unisept B*.

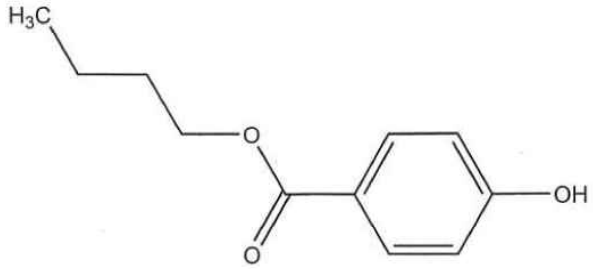
3 Chemical Name and CAS Registry Number

Butyl-4-hydroxybenzoate [94-26-8]

4 Empirical Formula and Molecular Weight

$C_{11}H_{14}O_3$ 194.23

5 Structural Formula



6 Functional Category

Antimicrobial preservative.

7 Applications in Pharmaceutical Formulation or Technology

Butylparaben is widely used as an antimicrobial preservative in cosmetics and pharmaceutical formulations; *see* Table I.

It may be used either alone or in combination with other paraben esters or with other antimicrobial agents. In cosmetics, it is the fourth most frequently used preservative.[1]

As a group, the parabens are effective over a wide pH range and have a broad spectrum of antimicrobial activity, although they are most effective against yeasts and molds; *see* Section 10.

Owing to the poor solubility of the parabens, paraben salts, particularly the sodium salt, are frequently used in formulations. However, this may raise the pH of poorly buffered formulations.

See Methylparaben for further information.

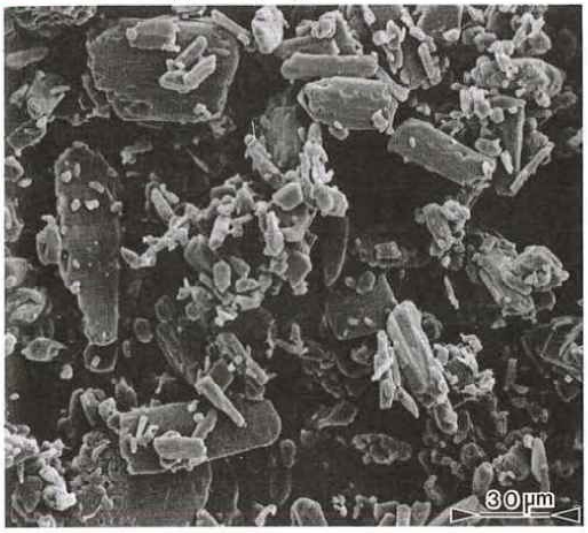
Table I: Uses of butylparaben.

Use	Concentration (%)
Oral suspensions	0.006–0.05
Topical preparations	0.02–0.4

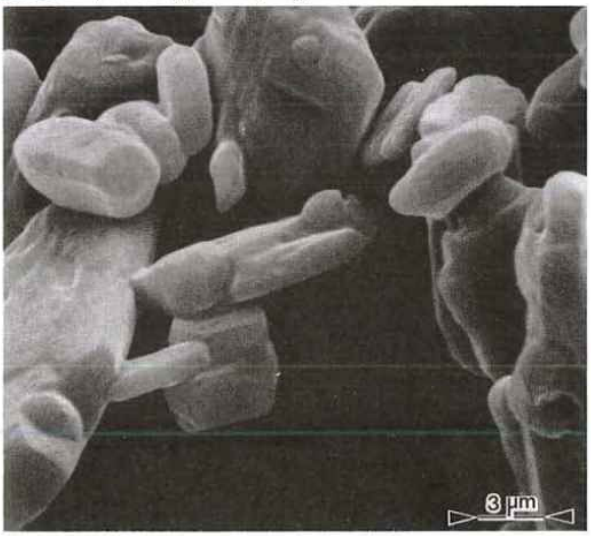
8 Description

Butylparaben occurs as colorless crystals or a white, crystalline, odorless or almost odorless, tasteless powder.

SEM 1: Excipient: butylparaben; magnification: 240×.



SEM 2: Excipient: butylparaben; magnification: 2400×.



9 Pharmacopeial Specifications

See Table II. *See also* Section 18.

Table II: Pharmacopeial specifications for butylparaben.

Test	JP XV	PhEur 6.0	USP32–NF27
Identification	+	+	+
Characters	+	+	–
Appearance of solution	+	+	+
Melting range	68–71°C	68–71°C	68–71°C
Acidity	+	+	+
Residue on ignition	≤0.1%	–	≤0.1%
Sulfated ash	–	≤0.1%	–
Related substances	+	+	+
Heavy metals	≤20 ppm	–	–
Assay (dried basis)	98.0–102.0%	98.0–102.0%	98.0–102.0%

10 Typical Properties

Antimicrobial activity Butylparaben exhibits antimicrobial activity between pH 4–8. Preservative efficacy decreases with increasing pH owing to the formation of the phenolate anion. Parabens are more active against yeasts and molds than against bacteria. They are also more active against Gram-positive than against Gram-negative bacteria; *see* Table III.[2]

The activity of the parabens increases with increasing chain length of the alkyl moiety, but solubility decreases. Butylparaben is thus more active than methylparaben. Activity may be improved by using combinations of parabens since synergistic effects occur. Activity has also been reported to be improved by the addition of other excipients; *see* Methylparaben for further information.

Table III: Minimum inhibitory concentrations (MICs) for butylparaben in aqueous solution.[2]

Microorganism	MIC (µg/mL)
Aerobacter aerogenes ATCC 8308	400
Aspergillus niger ATCC 9642	125
Aspergillus niger ATCC 10254	200
Bacillus cereus var. *mycoides* ATCC 6462	63
Bacillus subtilis ATCC 6633	250
Candida albicans ATCC 10231	125
Enterobacter cloacae ATCC 23355	250
Escherichia coli ATCC 8739	5000
Escherichia coli ATCC 9637	5000
Klebsiella pneumoniae ATCC 8308	250
Penicillium chrysogenum ATCC 9480	70
Penicillium digitatum ATCC 10030	32
Proteus vulgaris ATCC 13315	125
Pseudomonas aeruginosa ATCC 9027	>1000
Pseudomonas aeruginosa ATCC 15442	>1000
Pseudomonas stutzeri	500
Rhizopus nigricans ATCC 6227A	63
Saccharomyces cerevisiae ATCC 9763	35
Salmonella typhosa ATCC 6539	500
Serratia marcescens ATCC 8100	500
Staphylococcus aureus ATCC 6538P	125
Staphylococcus epidermidis ATCC 12228	250
Trichophyton mentagrophytes	35

Density (bulk) 0.731 g/cm^3
Density (tapped) 0.819 g/cm^3
Melting point 68–71°C
NIR spectra *see* Figure 1.
Partition coefficients Values for different vegetable oils vary considerably and are affected by the purity of the oil; *see* Table IV.[3]
Solubility *see* Table V.

Table IV: Partition coefficients for butylparaben between oils and water.[3]

Solvent	Partition coefficient oil : water
Mineral oil	3.0
Peanut oil	280
Soybean oil	280

11 Stability and Storage Conditions

Aqueous butylparaben solutions at pH 3–6 can be sterilized by autoclaving, without decomposition.[4] At pH 3–6, aqueous solutions are stable (less than 10% decomposition) for up to about 4 years at room temperature, while solutions at pH 8 or above are subject to rapid hydrolysis (10% or more after about 60 days at room temperature).[5]

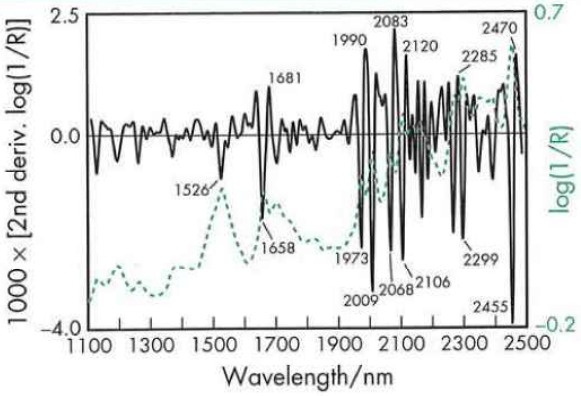


Figure 1: Near-infrared spectrum of butylparaben measured by reflectance.

Table V: Solubility of butylparaben.

Solvent	Solubility at 20°C unless otherwise stated
Acetone	Freely soluble
Ethanol	1 in 0.5
Ethanol (95%)	Freely soluble
Ether	Freely soluble
Glycerin	1 in 330
Methanol	1 in 0.5
Mineral oil	1 in 1000
Peanut oil	1 in 20
Propylene glycol	1 in 1
Water	1 in >5000 1 in 670 at 80°C

Butylparaben should be stored in a well-closed container, in a cool, dry place.

12 Incompatibilities

The antimicrobial activity of butylparaben is considerably reduced in the presence of nonionic surfactants as a result of micellization.[6] Absorption of butylparaben by plastics has not been reported but appears probable given the behavior of other parabens. Some pigments, e.g. ultramarine blue and yellow iron oxide, absorb butylparaben and thus reduce its preservative properties.[7]

Butylparaben is discolored in the presence of iron and is subject to hydrolysis by weak alkalis and strong acids.

See also Methylparaben.

13 Method of Manufacture

Butylparaben is prepared by esterification of *p*-hydroxybenzoic acid with *n*-butanol.

14 Safety

Butylparaben and other parabens are widely used as antimicrobial preservatives in cosmetics and oral and topical pharmaceutical formulations.

Systemically, no adverse reactions to parabens have been reported, although they have been associated with hypersensitivity reactions generally appearing as contact dermatitis. Immediate reactions with urticaria and bronchospasm have occurred rarely. *See* Methylparaben for further information.

LD_{50} (mouse, IP): 0.23 g/kg[8]

LD_{50} (mouse, oral): 13.2 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Butylparaben may be irritant to the skin, eyes, and mucous membranes, and should be handled in a well-ventilated environment. Eye protection, gloves, and a dust mask or respirator are recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Database (injections; oral capsules, solutions, suspensions, syrups and tablets; rectal, and topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Butylparaben sodium; ethylparaben; methylparaben; propylparaben.

Butylparaben sodium

Empirical formula $C_{11}H_{13}NaO_3$
Molecular weight 216.23
CAS number [36457-20-2]
Synonyms Butyl-4-hydroxybenzoate sodium salt; sodium butyl hydroxybenzoate.
Appearance White, odorless or almost odorless, hygroscopic powder.
Acidity/alkalinity pH = 9.5–10.5 (0.1% w/v aqueous solution)
Solubility 1 in 10 of ethanol (95%); 1 in 1 of water.
Comments Butylparaben sodium may be used instead of butylparaben because of its greater aqueous solubility. In unbuffered formulations, pH adjustment may be required.

18 Comments

Butylparaben is one of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter <1196> in the USP32–NF27, the General Chapter 5.8 in PhEur 6.0, along with the 'State of Work' document on the PhEur EDQM website, and also the General Information Chapter 8 in the JP XV.

See Methylparaben for further information and references.

The EINECS number for butylparaben is 202-318-7. The PubChem Compound ID (CID) for butylparaben is 7184.

19 Specific References

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See also Methylparaben.

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See also Methylparaben.

21 Author

S Gold.

22 Date of Revision

3 February 2009.

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3 Allen LV. Featured excipient: capsule and tablet diluents. *Int J Pharm Compound* 2000; 4(4): 306–310324–325.
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21 Author

NA Armstrong.

22 Date of Revision

16 January 2009.

Dextrin

1 Nonproprietary Names

BP: Dextrin
JP: Dextrin
PhEur: Dextrin
USP-NF: Dextrin

2 Synonyms

Avedex; British gum; *Caloreen*; canary dextrin; *C*Pharm*; *Crystal Gum*; dextrinum; dextrinum album; *Primogran W*; starch gum; yellow dextrin; white dextrin.

3 Chemical Name and CAS Registry Number

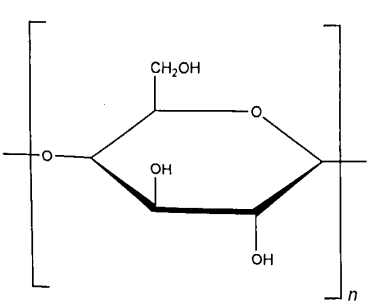
Dextrin [9004-53-9]

4 Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n{\cdot}xH_2O$ $(162.14)n$

The molecular weight of dextrin is typically 4500–85 000 and depends on the number of $(C_6H_{10}O_5)$ units in the polymer chain.

5 Structural Formula



6 Functional Category

Stiffening agent; suspending agent; tablet binder; tablet and capsule diluent.

7 Applications in Pharmaceutical Formulation or Technology

Dextrin is a dextrose polymer used as an adhesive and stiffening agent for surgical dressings. It is also used as a tablet and capsule diluent; as a binder for tablet granulation; as a sugar-coating ingredient that serves as a plasticizer and adhesive; and as a thickening agent for suspensions.

Additionally, dextrin has been used as a source of carbohydrate by people with special dietary requirements because it has a low electrolyte content and is free of lactose and sucrose.[1]

Dextrin is also used in cosmetics.

8 Description

Dextrin is partially hydrolyzed maize (corn), potato or cassava starch. It is a white, pale yellow or brown-colored powder with a slight characteristic odor.

9 Pharmacopeial Specifications

See Table I.

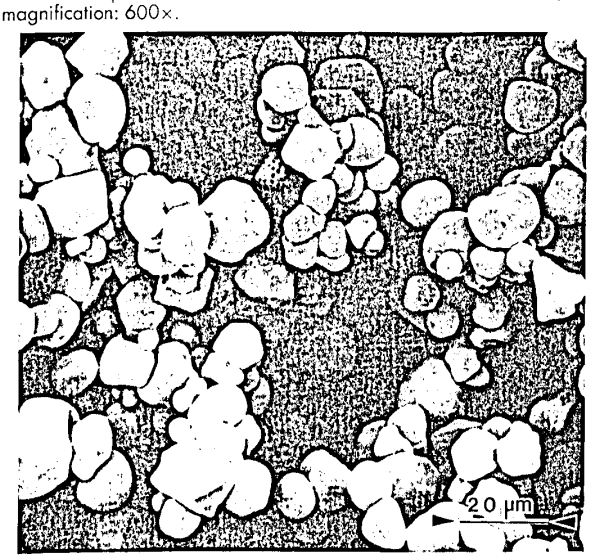
10 Typical Properties

Acidity/alkalinity pH = 2.8–8.0 for a 5% w/v aqueous solution.
Density (bulk) 0.80 g/cm^3
Density (tapped) 0.91 g/cm^3
Density (true) 1.495–1.589 g/cm^3
Melting point 178°C (with decomposition)
Moisture content 5% w/w
NIR spectra *see* Figure 1.
Particle size distribution *see* Figure 2.
Solubility Practically insoluble in chloroform, ethanol (95%), ether, and propan-2-ol; slowly soluble in cold water; very soluble in boiling water, forming a mucilaginous solution.
Specific surface area 0.14 m^2/g

11 Stability and Storage Conditions

Physical characteristics of dextrin may vary slightly depending on the method of manufacture and on the source material. In aqueous solutions, dextrin molecules tend to aggregate as density, tempera-

SEM 1: Excipient: dextrin; manufacturer: Matheson Colleman & Bell; magnification: 600×.



SEM 2: Excipient: dextrin; manufacturer: Matheson Colleman & Bell; magnification: 2400×.

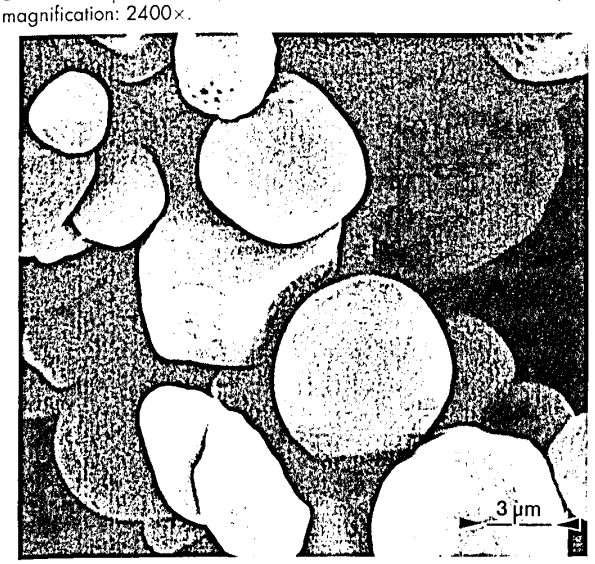


Table I: Pharmacopeial specifications for dextrin.

Test	JP XV	PhEur 6.4	USP32–NF27
Identification	+	+	+
Characters	–	+	–
Appearance of solution	+	–	–
Loss on drying	≤10.0%	≤13.0%	≤13.0%
Acidity	+	–	+
pH	–	2.0–8.0	–
Residue on ignition	≤0.5%	≤0.5%	≤0.5%
Chloride	≤0.013%	≤0.2%	≤0.2%
Sulfate	≤0.019%	–	–
Oxalate	+	–	–
Calcium	+	–	–
Heavy metals	≤50 ppm	≤20 ppm	≤20 µg/g
Protein	–	–	≤1.0%
Reducing sugars/ substances (calculated as $C_6H_{12}O_6$)	–	≤10.0%	≤10.0%

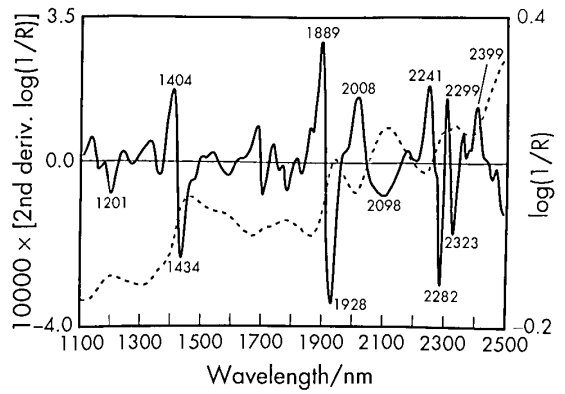


Figure 1: Near-infrared spectrum of dextrin measured by reflectance.

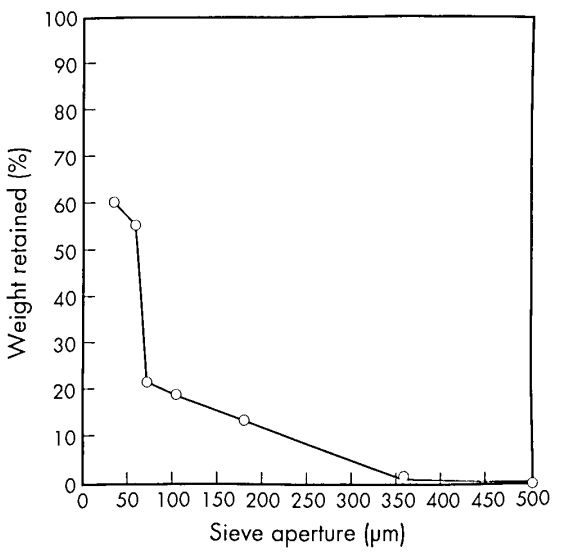


Figure 2: Particle size distribution of dextrin.

ture, pH, or other characteristics change. An increase in viscosity is caused by gelation or retrogradation as dextrin solutions age, and is particularly noticeable in the less-soluble maize starch dextrins. Dextrin solutions are thixotropic, becoming less viscous when sheared but changing to a soft paste or gel when allowed to stand. However, acids that are present in dextrin as residues from manufacturing can cause further hydrolysis, which results in a gradual thinning of solutions. Residual acid, often found in less-soluble dextrins such as pyrodextrin, will also cause a reduction in viscosity during dry storage. To eliminate these problems, dextrin manufacturers neutralize dextrins of low solubility with ammonia or sodium carbonate in the cooling vessel.

The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Incompatible with strong oxidizing agents.

13 Method of Manufacture

Dextrin is prepared by the incomplete hydrolysis of starch by heating in the dry state with or without the aid of suitable acids and buffers; moisture may be added during heating. The PhEur 6.4

specifies that dextrin is derived from maize (corn), potato or cassava starch. A specification for cassava is included in the USP32–NF27.

14 Safety

Dextrin is generally regarded as a nontoxic and nonirritant material at the levels employed as an excipient. Larger quantities are used as a dietary supplement without adverse effects, although ingestion of very large quantities may be harmful.

LD_{50} (mouse, IV): 0.35 g/kg[2]

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Dextrin may be irritant to the eyes. Eye protection, gloves, and a dust mask are recommended.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Database (IV injections, oral tablets and topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Dextrates; dextrose; glucose liquid; maltodextrin.
See also Section 18.

18 Comments

Dextrin is available from suppliers in a number of modified forms and mixtures such as dextrimaltose, a mixture of maltose and dextrin obtained by the enzymatic action of barley malt on corn flour. It is a light, amorphous powder, readily soluble in milk or water.

Crystal Gum is a grade of dextrin containing carbohydrate not less than 98% of dry weight. *Caloreen* [1] is a water-soluble mixture of dextrins consisting predominantly of polysaccharides containing an average of 5 dextrose molecules, with a mean molecular weight of 840, that does not change after heating. A 22% w/v solution of *Caloreen* is isoosmotic with serum.

A specification for dextrin is contained in the Food Chemicals Codex (FCC).[3]

The EINECS number for dextrin is 232-675-4. The PubChem Compound ID (CID) for dextrin is 62698.

19 Specific References

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21 Author

A Day.

22 Date of Revision

18 February 2009.

Dextrose

1 Nonproprietary Names

BP: Glucose
JP: Glucose
PhEur: Glucose Monohydrate
USP: Dextrose

2 Synonyms

Blood sugar; *Caridex*; corn sugar; *C*PharmDex*; *Dextrofin*; D-(+)-glucopyranose monohydrate; glucosum monohydricum; grape sugar; *Lycadex PF*; *Roferose*; starch sugar; *Tabfine D-100.*

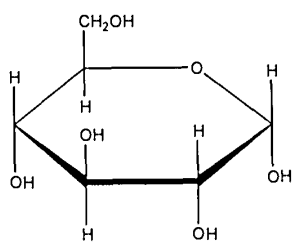
3 Chemical Name and CAS Registry Number

D-(+)-Glucose monohydrate [5996-10-1]
See also Section 17.

4 Empirical Formula and Molecular Weight

$C_6H_{12}O_6 \cdot H_2O$ 198.17 (for monohydrate)
See also Section 17.

5 Structural Formula



Anhydrous material shown.

6 Functional Category

Tablet and capsule diluent; therapeutic agent; tonicity agent; sweetening agent.

7 Applications in Pharmaceutical Formulation or Technology

Dextrose is widely used in solutions to adjust tonicity and as a sweetening agent. Dextrose is also used as a wet granulation diluent and binder, and as a direct-compression tablet diluent and binder,

LD_{50} (mouse, IV): 3.02 g/kg
LD_{50} (mouse, SC): 9.6 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of the material handled. Dimethylacetamide can be absorbed into the bloodstream by inhalation and through the skin; it is irritating to the skin and eyes.

16 Regulatory Status

Included in the FDA Inactive Ingredients Database (IM injections, IV injections and infusions). Included in parenteral medicines licensed in the UK.

17 Related Substances

—

18 Comments

A specification for dimethylacetamide is included in the *Japanese Pharmaceutical Excipients* (JPE).[12]

The EINECS number for dimethylacetamide is 204-826-4. The PubChem Compound ID (CID) for dimethylacetamide is 31374.

19 Specific References

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8 Anschel J. [Solvents and solubilization in injections.] *Pharm Ind* 1965; **27**: 781–787[in German].
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21 Author

RT Guest.

22 Date of Revision

17 October 2008.

Disodium Edetate

1 Nonproprietary Names

BP: Disodium Edetate
JP: Disodium Edetate Hydrate
PhEur: Disodium Edetate
USP: Edetate Disodium

2 Synonyms

Dinatrii edetas; disodium EDTA; disodium ethylenediaminetetraacetate; edathamil disodium; edetate disodium; edetic acid, disodium salt.

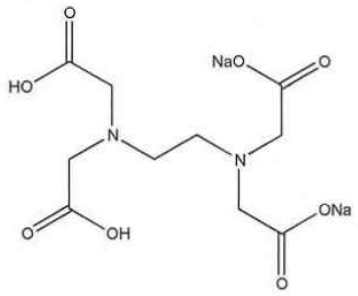
3 Chemical Name and CAS Registry Number

Ethylenediaminetetraacetic acid, disodium salt [139-33-3]
Disodium ethylenediaminetetraacetate dihydrate [6381-92-6]

4 Empirical Formula and Molecular Weight

$C_{10}H_{14}N_2Na_2O_8$ 336.2 (for anhydrous)
$C_{10}H_{18}N_2Na_2O_{10}$ 372.2 (for dihydrate)

5 Structural Formula



6 Functional Category

Chelating agent.

7 Applications in Pharmaceutical Formulation or Technology

Disodium edetate is used as a chelating agent in a wide range of pharmaceutical preparations, including mouthwashes, ophthalmic preparations, and topical preparations,[1–3] typically at concentrations between 0.005 and 0.1% w/v.

Disodium edetate forms stable water-soluble complexes (chelates) with alkaline earth and heavy-metal ions. The chelated form has few of the properties of the free ion, and for this reason chelating agents are often described as 'removing' ions from solution, a process known as sequestering. The stability of the metal–edetate complex is dependent on the metal ion involved and the pH.

Disodium edetate is also used as a water softener as it will chelate calcium and magnesium ions present in hard water. It is also used therapeutically as an anticoagulant as it will chelate calcium and prevent the coagulation of blood *in vitro*. Concentrations of 0.1% w/v are used in small volumes for hematological testing and 0.3% w/v in transfusions.

See also Edetic acid.

8 Description

Disodium edetate occurs as a white crystalline, odorless powder with a slightly acidic taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for disodium edetate.

Test	JP XV	PhEur 6.0	USP 32
Identification	+	+	+
Characters	+	+	–
Appearance of solution	+	+	–
pH	4.3–4.7	4.0–5.5	4.0–6.0
Iron	–	≤80 ppm	–
Calcium	–	–	+
Heavy metals	≤10 ppm	≤20 ppm	≤0.005%
Cyanide	+	–	–
Arsenic	≤2 ppm	–	–
Limit of nitrilotriacetic acid	–	≤0.1%	≤0.1%
Residue on ignition	37.0–39.0%	–	–
Loss on drying	–	–	8.7–11.4%
Assay	≥99.0%	98.5–101.0%	99.0–101.0%

10 Typical Properties

Acidity/alkalinity pH 4.3–4.7 (1% w/v solution in carbon dioxide-free water)
Freezing point depression 0.14°C (1% w/v aqueous solution)
Melting point Decomposition at 252°C for the dihydrate.
NIR spectra *see* Figure 1.
Refractive index 1.33 (1% w/v aqueous solution)
Solubility Practically insoluble in chloroform and ether; slightly soluble in ethanol (95%); soluble 1 part in 11 parts water.
Specific gravity 1.004 (1% w/v aqueous solution)
Viscosity (kinematic) 1.03 mm^2/s (1.03 cSt) (1% w/v aqueous solution).

11 Stability and Storage Conditions

Edetate salts are more stable than edetic acid (*see also* Edetic acid). However, disodium edetate dihydrate loses water of crystallization when heated to 120°C. Aqueous solutions of disodium edetate may be sterilized by autoclaving, and should be stored in an alkali-free container.

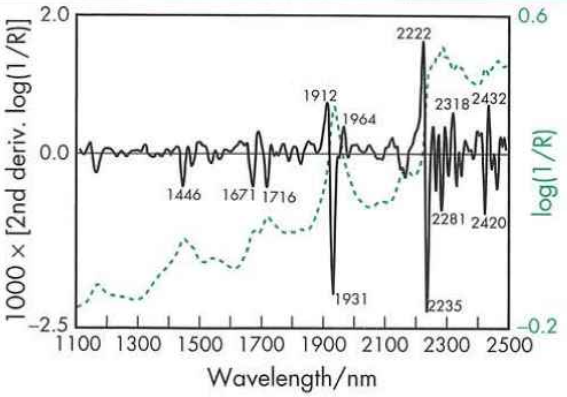


Figure 1: Near-infrared spectrum of disodium edetate dihydrate measured by reflectance.

Disodium edetate is hygroscopic and is unstable when exposed to moisture. It should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Disodium edetate behaves as a weak acid, displacing carbon dioxide from carbonates and reacting with metals to form hydrogen. It is incompatible with strong oxidizing agents, strong bases, metal ions, and metal alloys.

See also Edetic acid.

13 Method of Manufacture

Disodium edetate may be prepared by the reaction of edetic acid and sodium hydroxide.

14 Safety

Disodium edetate is used widely in topical, oral, and parenteral pharmaceutical formulations; it is used extensively in cosmetic and food products. Disodium edetate and edetate calcium disodium are used in a greater number and variety of pharmaceutical formulations than is edetic acid. Both disodium edetate and edetate calcium disodium are poorly absorbed from the gastrointestinal tract and are associated with few adverse effects when used as excipients in pharmaceutical formulations.

Disodium edetate, trisodium edetate, and edetic acid readily chelate calcium and can, in large doses, cause calcium depletion (hypocalcemia) if used over an extended period of time, or if administered too rapidly by intravenous infusion. If used in preparations for the mouth, they can also leach calcium from the teeth. However, edetate calcium disodium does not chelate calcium.

Disodium edetate should be used with caution in patients with renal impairment, tuberculosis, and impaired cardiac function.

Although disodium edetate is generally considered safe, there have been reports of disodium edetate toxicity in patients receiving chelation therapy.[4]

Nasal formulations containing benzalkonium chloride and disodium edetate, both known to be local irritants, were shown to produce an inflammatory reaction, and microscopic examination showed an extended infiltration of the mucosa by eosinophils, and pronounced atrophy and disorganization of the epithelium, although these effects were subsequently shown to be reversible.[3]

The WHO has set an estimated acceptable daily intake for disodium EDTA in foodstuffs of up to 2.5 mg/kg body-weight.[5] *See also* Edetic acid.

LD_{50} (mouse, IP): 0.26 g/kg[6]
LD_{50} (mouse, IV): 0.056 g/kg

LD_{50} (mouse, OP): 2.05 g/kg
LD_{50} (rabbit, IV): 0.047 g/kg
LD_{50} (rabbit, OP): 2.3 g/kg
LD_{50} (rat, OP): 2.0 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Disodium edetate and its derivatives are mild irritants to the mucous membranes. Eye protection, gloves, and dust masks are recommended.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Database (inhalations; injections; ophthalmic preparations; oral capsules, solutions, suspensions, syrups, and tablets; rectal topical, and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Edetic acid.

18 Comments

Disodium edetate has been used experimentally to investigate the stability and skin penetration capacity of captopril gel, in which disodium edetate was shown to exert a potent stabilizing effect, and may be used in the development of a transdermal drug delivery system.[7]

A chitosan–EDTA conjugate has been investigated as a novel polymer for use in topical gels. The conjugate was shown to be stable, colorless, and transparent, and it also demonstrated antimicrobial effects.[8]

The EINECS number for disodium edetate is 205-358-3. The PubChem Compound ID (CID) for disodium edetate includes 8759 and 636371.

19 Specific References

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8 Valenta C *et al.* Chitosan–EDTA conjugate: novel polymer for topical gels. *J Pharm Pharmacol* 1998; **50**: 445–452.

20 General References

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21 Authors

S Shah, D Thassu.

22 Date of Revision

30 January 2009.

Docusate Sodium

1 Nonproprietary Names

BP: Docusate Sodium
PhEur: Docusate Sodium
USP: Docusate Sodium

2 Synonyms

Bis(2-ethylhexyl) sodium sulfosuccinate; dioctyl sodium sulfosuccinate; DSS; natrii docusas; sodium 1,4-bis(2-ethylhexyl) sulfosuccinate; sodium 1,4-bis[(2-ethylhexyl)oxy]-1,4-dioxobutane-2-sulfonate; sodium dioctyl sulfosuccinate; sulfo-butanedioic acid 1,4-bis(2-ethylhexyl) ester, sodium salt; sulfosuccinic acid 1,4-bis(2-ethylhexyl) ester *S*-sodium salt.

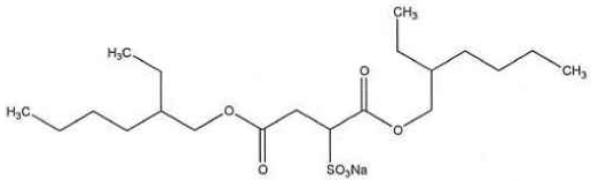
3 Chemical Name and CAS Registry Number

Sodium 1,4-bis(2-ethylhexyl) sulfosuccinate [577-11-7]

4 Empirical Formula and Molecular Weight

$C_{20}H_{37}NaO_7S$ 444.56

5 Structural Formula



6 Functional Category

Anionic surfactant; fecal softener; wetting agent.

7 Applications in Pharmaceutical Formulation or Technology

Docusate sodium and docusate salts are widely used as anionic surfactants in pharmaceutical formulations. Docusate sodium is mainly used in capsule and direct-compression tablet formulations to assist in wetting and dissolution.[1] Docusate salts are also used in oral formulations as laxatives and fecal softeners; *see* Table I.

Ethylparaben

1 Nonproprietary Names

BP: Ethyl Hydroxybenzoate
JP: Ethyl Parahydroxybenzoate
PhEur: Ethyl Parahydroxybenzoate
USP-NF: Ethylparaben

2 Synonyms

Aethylum hydrobenzoicum; *CoSept E*; E214; ethylis parahydroxybenzoas; ethyl *p*-hydroxybenzoate; *Ethyl parasept*; 4-hydroxybenzoic acid ethyl ester; *Nipagin A*; *Solbrol A*; *Tegosept E*; *Uniphen P-23*.

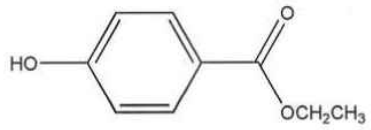
3 Chemical Name and CAS Registry Number

Ethyl-4-hydroxybenzoate [120-47-8]

4 Empirical Formula and Molecular Weight

$C_9H_{10}O_3$ 166.18

5 Structural Formula



6 Functional Category

Antimicrobial preservative.

7 Applications in Pharmaceutical Formulation or Technology

Ethylparaben is widely used as an antimicrobial preservative in cosmetics,[1] food products, and pharmaceutical formulations.

It may be used either alone or in combination with other paraben esters or with other antimicrobial agents. In cosmetics it is one of the most frequently used preservatives.

The parabens are effective over a wide pH range and have a broad spectrum of antimicrobial activity, although they are most effective against yeasts and molds; *see* Section 10.

Owing to the poor solubility of the parabens, paraben salts, particularly the sodium salt, are frequently used. However, this may cause the pH of poorly buffered formulations to become more alkaline.

See Methylparaben for further information.

8 Description

Ethylparaben occurs as a white, odorless or almost odorless, crystalline powder.

9 Pharmacopeial Specifications

See Table I. *See also* Section 18.

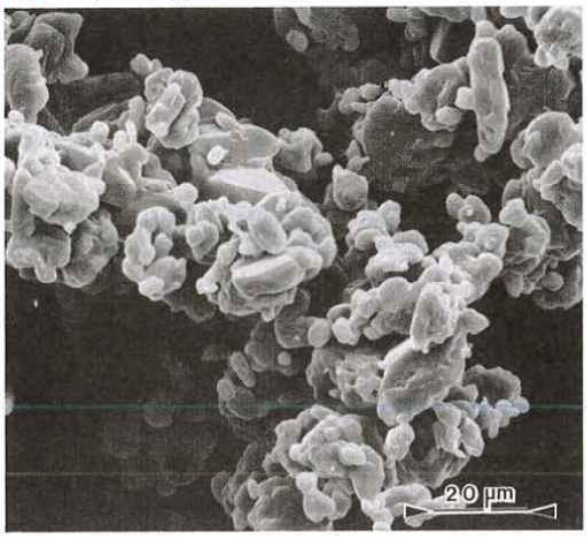
10 Typical Properties

Antimicrobial activity

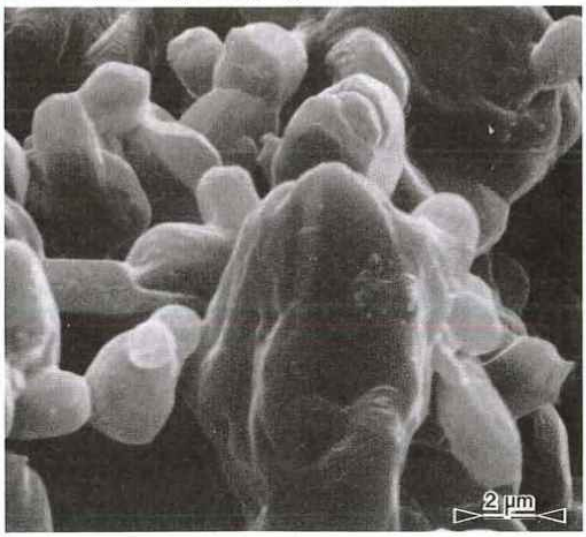
Ethylparaben exhibits antimicrobial activity from pH 4–8. Preservative efficacy decreases with increasing pH owing to the formation of the phenolate anion. Parabens are more active against yeasts and molds than against bacteria. They are also more active against Gram-positive than against Gram-negative bacteria.

The activity of the parabens increases with increasing chain length of the alkyl moiety, but solubility decreases. Activity may be improved by using combinations of parabens since synergistic effects occur. Ethylparaben is commonly used with methylparaben and propylparaben in oral and topical formulations (such mixtures are commercially available; for example, *Nipasept* (Nipa Laboratories Inc.). Activity has also been reported to be improved by the addition of other excipients; *see* Methylparaben for further information.

SEM 1: Excipient: ethylparaben; magnification: 600×.



SEM 2: Excipient: ethylparaben; magnification: 3000×.



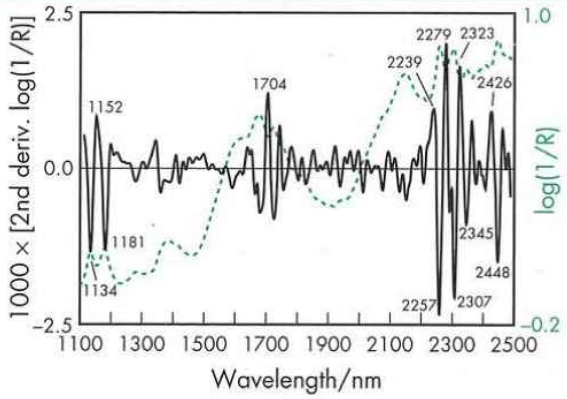


Figure 1: Near-infrared spectrum of ethylparaben measured by reflectance.

Table I: Pharmacopeial specifications for ethylparaben.

Test	JP XV	PhEur 6.0	USP32–NF27
Identification	+	+	+
Appearance of solution	+	+	+
Characters	–	+	–
Heavy metals	⩽20 ppm	–	–
Acidity	+	+	+
Melting range	115–118°C	–	115–118°C
Related substances	+	+	+
Residue on ignition	⩽0.1%	⩽0.1%	⩽0.1%
Assay (dried basis)	98.0–102.0%	98.0–102.0%	98.0–102.0%

See Table II for minimum inhibitory concentrations of ethylparaben.[2]

Boiling point 297–298°C with decomposition.

Melting point 115–118°C

NIR spectra *see* Figure 1.

Partition coefficient The values for different vegetable oils vary considerably and are affected by the purity of the oil; *see* Table III.[3]

Solubility *see* Table IV.

11 Stability and Storage Conditions

Aqueous ethylparaben solutions at pH 3–6 can be sterilized by autoclaving, without decomposition.[4] At pH 3–6, aqueous solutions are stable (less than 10% decomposition) for up to about 4 years at room temperature, while solutions at pH 8 or above are subject to rapid hydrolysis (10% or more after about 60 days at room temperature).[5]

Ethylparaben should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

The antimicrobial properties of ethylparaben are considerably reduced in the presence of nonionic surfactants as a result of micellization.[6] Absorption of ethylparaben by plastics has not been reported, although it appears probable given the behavior of other parabens. Ethylparaben is coabsorbed on silica in the presence of ethoxylated phenols.[7] Yellow iron oxide, ultramarine blue, and aluminum silicate extensively absorb ethylparaben in simple aqueous systems, thus reducing preservative efficacy.[8,9]

Ethylparaben is discolored in the presence of iron and is subject to hydrolysis by weak alkalis and strong acids.

See also Methylparaben.

Table II: Minimum inhibitory concentrations (MICs) for ethylparaben in aqueous solution.[2]

Microorganism	MIC (μg/mL)
Aerobacter aerogenes ATCC 8308	1200
Aspergillus niger ATCC 9642	500
Aspergillus niger ATCC 10254	400
Bacillus cereus var. *mycoides* ATCC 6462	1000
Bacillus subtilis ATCC 6633	1000
Candida albicans ATCC 10231	500
Enterobacter cloacae ATCC 23355	1000
Escherichia coli ATCC 8739	1000
Escherichia coli ATCC 9637	1000
Klebsiella pneumoniae ATCC 8308	500
Penicillium chrysogenum ATCC 9480	250
Penicillium digitatum ATCC 10030	250
Proteus vulgaris ATCC 13315	500
Pseudomonas aeruginosa ATCC 9027	>2000
Pseudomonas aeruginosa ATCC 15442	>2000
Pseudomonas stutzeri	1000
Rhizopus nigricans ATCC 6227A	250
Saccharomyces cerevisiae ATCC 9763	500
Salmonella typhosa ATCC 6539	1000
Serratia marcescens ATCC 8100	1000
Staphylococcus aureus ATCC 6538P	1000
Staphylococcus epidermidis ATCC 12228	1000
Trichophyton mentagrophytes	125

Table III: Partition coefficients for ethylparaben in vegetable oil and water.[3]

Solvent	Partition coefficient oil : water
Corn oil	14.0
Mineral oil	0.13
Peanut oil	16.1
Soybean oil	18.8

Table IV: Solubility of ethylparaben in various solvents.

Solvent	Solubility at 20°C unless otherwise stated
Acetone	Freely soluble
Ethanol	1 in 1.4
Ethanol (95%)	1 in 2
Ether	1 in 3.5
Glycerin	1 in 200
Methanol	1 in 0.9
Mineral oil	1 in 4000
Peanut oil	1 in 100
Propylene glycol	1 in 4
Water	1 in 1250 at 15°C 1 in 910 1 in 120 at 80°C

13 Method of Manufacture

Ethylparaben is prepared by the esterification of *p*-hydroxybenzoic acid with ethanol (95%).

14 Safety

Ethylparaben and other parabens are widely used as antimicrobial preservatives in cosmetics, food products, and oral and topical pharmaceutical formulations.

Systemically, no adverse reactions to parabens have been reported, although they have been associated with hypersensitivity reactions. Parabens, *in vivo*, have also been reported to exhibit estrogenic responses in fish.[10] The WHO has set an estimated total acceptable daily intake for methyl-, ethyl-, and propylparabens at up to 10 mg/kg body-weight.[11]

LD_{50} (mouse, IP): 0.52 g/kg[12]
LD_{50} (mouse, oral): 3.0 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Ethylparaben may be irritant to the skin, eyes, and mucous membranes, and should be handled in a well ventilated environment. Eye protection, gloves, and a dust mask or respirator are recommended.

E

16 Regulatory Status

Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Database (oral, otic, and topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Butylparaben; ethylparaben potassium; ethylparaben sodium; methylparaben; propylparaben.

Ethylparaben potassium
Empirical formula $C_9H_9KO_3$
Molecular weight 204.28
CAS number [36547-19-9]
Synonyms Ethyl 4-hydroxybenzoate potassium salt; potassium ethyl hydroxybenzoate.

Ethylparaben sodium
Empirical formula $C_9H_9NaO_3$
Molecular weight 188.17
CAS number [35285-68-8]
Synonyms E215; ethyl 4-hydroxybenzoate sodium salt; sodium ethyl hydroxybenzoate.

18 Comments

Ethylparaben is one of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter <1196> in the USP32–NF27, the General Chapter 5.8 in PhEur 6.0, along with the 'State of Work' document on the PhEur EDQM website, and also the General Information Chapter 8 in the JP XV.

See Methylparaben for further information.

The EINECS number for ethylparaben is 204-399-4. The PubChem Compound ID (CID) for ethylparaben is 8434.

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21 Author

N Sandler.

22 Date of Revision

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21 Authors

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22 Date of Revision

3 February 2009.

Methylparaben

1 Nonproprietary Names

BP: Methyl Hydroxybenzoate
JP: Methyl Parahydroxybenzoate
PhEur: Methyl Parahydroxybenzoate
USP-NF: Methylparaben

2 Synonyms

Aseptoform M; *CoSept M*; E218; 4-hydroxybenzoic acid methyl ester; metagin; *Methyl Chemosept*; methylis parahydroxybenzoas; methyl *p*-hydroxybenzoate; *Methyl Parasept*; *Nipagin M*; *Solbrol M*; *Tegosept M*; *Uniphen P-23*.

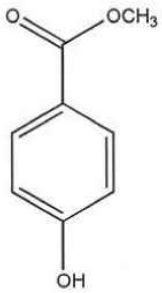
3 Chemical Name and CAS Registry Number

Methyl-4-hydroxybenzoate [99-76-3]

4 Empirical Formula and Molecular Weight

$C_8H_8O_3$ 152.15

5 Structural Formula



6 Functional Category

Antimicrobial preservative.

7 Applications in Pharmaceutical Formulation or Technology

Methylparaben is widely used as an antimicrobial preservative in cosmetics, food products, and pharmaceutical formulations; *see* Table I. It may be used either alone or in combination with other

parabens or with other antimicrobial agents. In cosmetics, methylparaben is the most frequently used antimicrobial preservative.[1]

The parabens are effective over a wide pH range and have a broad spectrum of antimicrobial activity, although they are most effective against yeasts and molds. Antimicrobial activity increases as the chain length of the alkyl moiety is increased, but aqueous solubility decreases; therefore a mixture of parabens is frequently used to provide effective preservation. Preservative efficacy is also improved by the addition of propylene glycol (2–5%), or by using parabens in combination with other antimicrobial agents such as imidurea; *see* Section 10.

Owing to the poor solubility of the parabens, paraben salts (particularly the sodium salt) are more frequently used in formulations. However, this raises the pH of poorly buffered formulations.

Methylparaben (0.18%) together with propylparaben (0.02%) has been used for the preservation of various parenteral pharmaceutical formulations; *see* Section 14.

Table I: Uses of methylparaben.

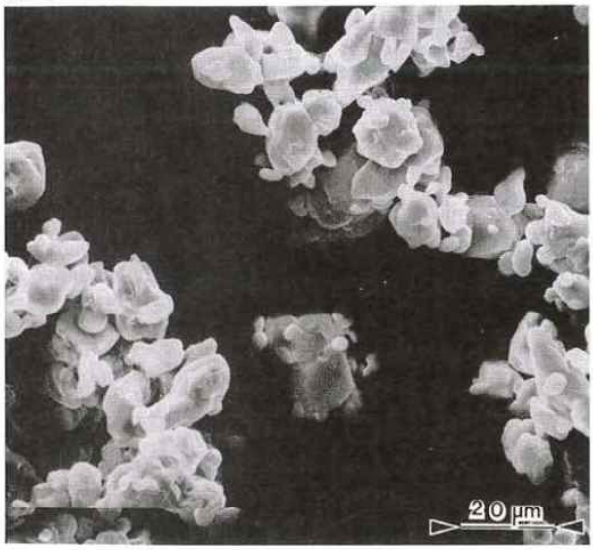
Use	Concentration (%)
IM, IV, SC injections[a]	0.065–0.25
Inhalation solutions	0.025–0.07
Intradermal injections	0.10
Nasal solutions	0.033
Ophthalmic preparations[a]	0.015–0.2
Oral solutions and suspensions	0.015–0.2
Rectal preparations	0.1–0.18
Topical preparations	0.02–0.3
Vaginal preparations	0.1–0.18

(a) *See* Section 14.

8 Description

Methylparaben occurs as colorless crystals or a white crystalline powder. It is odorless or almost odorless and has a slight burning taste.

SEM 1: Excipient: methylparaben; supplier: Bate Chemical Co. Ltd; magnification: 600×.



9 Pharmacopeial Specifications

See Table II. *See also* Section 18.

Table II: Pharmacopeial specifications for methylparaben.

Test	JP XV	PhEur 6.0	USP32–NF27
Identification	+	+	+
Characters	–	+	–
Appearance of solution	+	+	+
Acidity	+	+	+
Heavy metals	⩽20 ppm	–	–
Impurities	–	+	–
Melting range	–	–	125–128°C
Related substances	+	+	+
Sulfated ash	–	⩽0.1%	–
Residue on ignition	⩽0.1%	–	⩽0.1%
Assay (dried basis)	98.0–102.0%	98.0–102.0%	98.0–102.0%

10 Typical Properties

Antimicrobial activity *see* Table III. Methylparaben exhibits antimicrobial activity of pH 4–8. Preservative efficacy decreases with increasing pH owing to the formation of the phenolate anion. Parabens are more active against yeasts and molds than against bacteria. They are also more active against Gram-positive bacteria than against Gram-negative bacteria.

Methylparaben is the least active of the parabens; antimicrobial activity increases with increasing chain length of the alkyl moiety. Activity may be improved by using combinations of parabens as synergistic effects occur. Therefore, combinations of methyl-, ethyl-, propyl-, and butylparaben are often used together. Activity has also been reported to be enhanced by the addition of other excipients such as: propylene glycol (2–5%);[2] phenylethyl alcohol;[3] and edetic acid.[4] Activity may also be enhanced owing to synergistic effects by using combinations of parabens with other antimicrobial preservatives such as imidurea.[5]

The hydrolysis product *p*-hydroxybenzoic acid has practically no antimicrobial activity.

See also Section 12.

Table III: Minimum inhibitory concentrations (MICs) of methylparaben in aqueous solution.[4]

Microorganism	MIC (µg/mL)
Aerobacter aerogenes ATCC 8308	2000
Aspergillus oryzae	600
Aspergillus niger ATCC 9642	1000
Aspergillus niger ATCC 10254	1000
Bacillus cereus var. *mycoides* ATCC 6462	2000
Bacillus subtilis ATCC 6633	2000
Candida albicans ATCC 10231	2000
Enterobacter cloacae ATCC 23355	1000
Escherichia coli ATCC 8739	1000
Escherichia coli ATCC 9637	1000
Klebsiella pneumoniae ATCC 8308	1000
Penicillium chrysogenum ATCC 9480	500
Penicillium digitatum ATCC 10030	500
Proteus vulgaris ATCC 8427	2000
Proteus vulgaris ATCC 13315	1000
Pseudomonas aeruginosa ATCC 9027	4000
Pseudomonas aeruginosa ATCC 15442	4000
Pseudomonas stutzeri	2000
Rhizopus nigricans ATCC 6227A	500
Saccharomyces cerevisiae ATCC 9763	1000
Salmonella typhosa ATCC 6539	1000
Sarcina lutea	4000
Serratia marcescens ATCC 8100	1000
Staphylococcus aureus ATCC 6538P	2000
Staphylococcus epidermidis ATCC 12228	2000
Trichoderma lignorum ATCC 8678	250
Trichoderma mentagrophytes	250

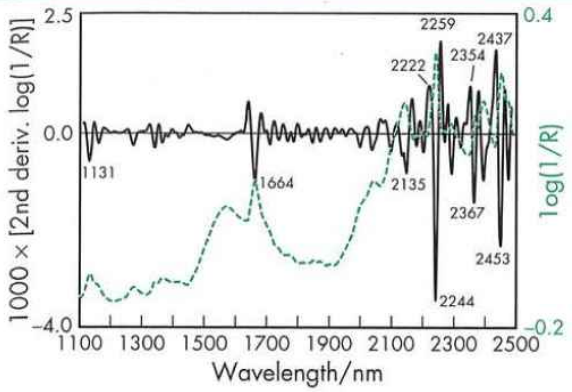


Figure 1: Near-infrared spectrum of methylparaben measured by reflectance.

Density (true) 1.352 g/cm^3
Dissociation constant pK_a = 8.4 at 22°C
Melting point 125–128°C
NIR spectra *see* Figure 1.
Partition coefficients Values for different vegetable oils vary considerably and are affected by the purity of the oil; *see* Table IV.
Solubility *see* Table V.

Table IV: Partition coefficients of methylparaben in vegetable oil and water.[6,7]

Solvent	Partition coefficient oil : water
Almond oil	7.5
Castor oil	6.0
Corn oil	4.1
Diethyl adipate	200
Isopropyl myristate	18.0
Lanolin	7.0
Mineral oil	0.1
Peanut oil	4.2
Soybean oil	6.1

Table V: Solubility of methylparaben in various solvents.[4]

Solvent	Solubility at 25°C unless otherwise stated
Ethanol	1 in 2
Ethanol (95%)	1 in 3
Ethanol (50%)	1 in 6
Ether	1 in 10
Glycerin	1 in 60
Mineral oil	Practically insoluble
Peanut oil	1 in 200
Propylene glycol	1 in 5
Water	1 in 400
	1 in 50 at 50°C
	1 in 30 at 80°C

11 Stability and Storage Conditions

Aqueous solutions of methylparaben at pH 3–6 may be sterilized by autoclaving at 120°C for 20 minutes, without decomposition.[8] Aqueous solutions at pH 3–6 are stable (less than 10% decomposition) for up to about 4 years at room temperature, while aqueous solutions at pH 8 or above are subject to rapid hydrolysis (10% or more after about 60 days storage at room temperature); *see* Tables VI and VII.[9]

Methylparaben should be stored in a well-closed container in a cool, dry place.

Table VI: Predicted rate constants and half-lives for methylparaben dissolved in dilute hydrochloric acid solution, at 25°C.

Initial pH of solution	Rate constant $k \pm \sigma^{(a)}$ (hour^{-1})	Half-life $t_{1/2} \pm \sigma^{(a)}$ (day)
1	$(1.086 \pm 0.005) \times 10^{-4}$	266 ± 13
2	$(1.16 \pm 0.12) \times 10^{-5}$	2490 ± 260
3	$(6.1 \pm 1.5) \times 10^{-7}$	47000 ± 12000
4	$(3.27 \pm 0.64) \times 10^{-7}$	88000 ± 17000

(a) Indicates the standard error.

Table VII: Predicted remaining amount of methylparaben dissolved in dilute hydrochloric acid solution, after autoclaving.

Initial pH of solution	Rate constant $k \pm \sigma^{(a)}$ (hour^{-1})	Predicted residual amount after autoclaving (%)
1	$(4.96 \pm 0.16) \times 10^{-1}$	84.77 ± 0.46
2	$(4.49 \pm 0.37) \times 10^{-2}$	98.51 ± 0.12
3	$(2.79 \pm 0.57) \times 10^{-3}$	99.91 ± 0.02
4	$(1.49 \pm 0.22) \times 10^{-3}$	99.95 ± 0.01

(a) Indicates the standard error.

12 Incompatibilities

The antimicrobial activity of methylparaben and other parabens is considerably reduced in the presence of nonionic surfactants, such as polysorbate 80, as a result of micellization.[10,11] However, propylene glycol (10%) has been shown to potentiate the antimicrobial activity of the parabens in the presence of nonionic surfactants and prevents the interaction between methylparaben and polysorbate 80.[12]

Incompatibilities with other substances, such as bentonite,[13] magnesium trisilicate,[14] talc, tragacanth,[15] sodium alginate,[16] essential oils,[17] sorbitol,[18] and atropine,[19] have been reported. It also reacts with various sugars and related sugar alcohols.[20]

Absorption of methylparaben by plastics has also been reported; the amount absorbed is dependent upon the type of plastic and the vehicle. It has been claimed that low-density and high-density polyethylene bottles do not absorb methylparaben.[21]

Methylparaben is discolored in the presence of iron and is subject to hydrolysis by weak alkalis and strong acids.

13 Method of Manufacture

Methylparaben is prepared by the esterification of *p*-hydroxybenzoic acid with methanol.

14 Safety

Methylparaben and other parabens are widely used as antimicrobial preservatives in cosmetics and oral and topical pharmaceutical formulations. Although parabens have also been used as preservatives in injections and ophthalmic preparations, they are now generally regarded as being unsuitable for these types of formulations owing to the irritant potential of the parabens. These experiences may depend on immune responses to enzymatically formed metabolites of the parabens in the skin.

Parabens are nonmutagenic, nonteratogenic, and noncarcinogenic. Sensitization to the parabens is rare, and these compounds do not exhibit significant levels of photocontact sensitization or phototoxicity.

Hypersensitivity reactions to parabens, generally of the delayed type and appearing as contact dermatitis, have been reported. However, given the widespread use of parabens as preservatives, such reactions are relatively uncommon; the classification of

parabens in some sources as high-rate sensitizers may be overstated.[22]

Immediate hypersensitivity reactions following injection of preparations containing parabens have also been reported.[23–25] Delayed-contact dermatitis occurs more frequently when parabens are used topically, but has also been reported to occur after oral administration.[26–28]

Unexpectedly, preparations containing parabens may be used by patients who have reacted previously with contact dermatitis provided they are applied to another, unaffected, site. This has been termed the paraben paradox.[29]

Concern has been expressed over the use of methylparaben in infant parenteral products because bilirubin binding may be affected, which is potentially hazardous in hyperbilirubinemic neonates.[30]

The WHO has set an estimated total acceptable daily intake for methyl-, ethyl-, and propylparabens at up to 10 mg/kg bodyweight.[31]

LD_{50} (dog, oral): 3.0 g/kg[32]

LD_{50} (mouse, IP): 0.96 g/kg

LD_{50} (mouse, SC): 1.20 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Methylparaben may be irritant to the skin, eyes, and mucous membranes, and should be handled in a well-ventilated environment. Eye protection, gloves, and a dust mask or respirator are recommended.

M

16 Regulatory Status

Methylparaben and propylparaben are affirmed GRAS Direct Food Substances in the USA at levels up to 0.1%. All esters except the benzyl ester are allowed for injection in Japan. In cosmetics, the EU and Brazil allow use of each paraben at 0.4%, but the total of all parabens may not exceed 0.8%. The upper limit in Japan is 1.0%.

Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (IM, IV, and SC injections; inhalation preparations; ophthalmic preparations; oral capsules, tablets, solutions and suspensions; otic, rectal, topical, and vaginal preparations). Included in medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Butylparaben; ethylparaben; methylparaben potassium; methylparaben sodium; propylparaben.

Methylparaben potassium

Empirical formula $C_8H_7KO_3$
Molecular weight 190.25
CAS number [26112-07-2]
Synonyms Methyl 4-hydroxybenzoate potassium salt; potassium methyl hydroxybenzoate.
Comments Methylparaben potassium may be used instead of methylparaben because of its greater aqueous solubility.

Methylparaben sodium

Empirical formula $C_8H_7NaO_3$
Molecular weight 174.14
CAS number [5026-62-0]
Synonyms E219; methyl 4-hydroxybenzoate sodium salt; sodium methyl hydroxybenzoate; soluble methyl hydroxybenzoate.
Appearance A white, odorless or almost odorless, hygroscopic crystalline powder.
Acidity/alkalinity pH = 9.5–10.5 (0.1% w/v aqueous solution)
Solubility 1 in 50 of ethanol (95%); 1 in 2 of water; practically insoluble in fixed oils.
Comments Methylparaben sodium may be used instead of methylparaben because of its greater aqueous solubility. However, it may cause the pH of a formulation to become more alkaline.

18 Comments

Methylparaben is one of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter <1196> in the USP32–NF27, the General Chapter 5.8 in PhEur 6.0, along with the 'State of Work' document on the PhEur EDQM website, and also the General Information Chapter 8 in the JP XV.

The BP 2009, Ph Eur 6.0 and USP32–NF27 also list Methylparaben Sodium as a separate monograph.

The EINECS number for methylparaben is 202-785-7. In addition to the most commonly used paraben esters, some other less-common esters have also been used; *see* Table VIII. A specification for methylparaben is contained in the Food Chemicals Codex (FCC).[33]

The PubChem Compound ID (CID) for methylparaben is 7456.

Table VIII: CAS numbers of less common paraben esters.

Name	CAS Number
Benzylparaben	94-18-8
Isobutylparaben	4247-02-3
Isopropylparaben	4191-73-5

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21 Author

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22 Date of Revision

3 February 2009.

Mineral Oil

1 Nonproprietary Names

BP: Liquid Paraffin
JP: Liquid Paraffin
PhEur: Paraffin, Liquid
USP: Mineral Oil

2 Synonyms

Avatech; *Drakeol*; heavy mineral oil; heavy liquid petrolatum; liquid petrolatum; paraffin oil; paraffinum liquidum; *Sirius*; white mineral oil.

3 Chemical Name and CAS Registry Number

Mineral oil [8012-95-1]

4 Empirical Formula and Molecular Weight

Mineral oil is a mixture of refined liquid saturated aliphatic (C_{14}–C_{18}) and cyclic hydrocarbons obtained from petroleum.

5 Structural Formula

See Section 4.

6 Functional Category

Emollient; lubricant; oleaginous vehicle; solvent; vaccine adjuvant.

7 Applications in Pharmaceutical Formulation or Technology

Mineral oil is used primarily as an excipient in topical pharmaceutical formulations, where its emollient properties are exploited as an ingredient in ointment bases; *see* Table I. It is additionally used in oil-in-water emulsions,[1–5] as a solvent, and as a lubricant in capsule and tablet formulations, and to a limited extent as a mold-

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RT Forbes, M Isreb.

22 Date of Revision

10 March 2009.

Polyethylene Glycol

1 Nonproprietary Names

BP: Macrogols
JP: Macrogol 400
Macrogol 1500
Macrogol 4000
Macrogol 6000
Macrogol 20000
PhEur: Macrogols
USP-NF: Polyethylene Glycol

2 Synonyms

Carbowax; *Carbowax Sentry*; *Lipoxol*; *Lutrol E*; macrogola; PEG; *Pluriol E*; polyoxyethylene glycol.

3 Chemical Name and CAS Registry Number

α-Hydro-ω-hydroxypoly(oxy-1,2-ethanediyl) [25322-68-3]

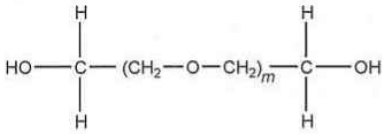
4 Empirical Formula and Molecular Weight

$HOCH_2(CH_2OCH_2)_mCH_2OH$ where m represents the average number of oxyethylene groups.

Alternatively, the general formula $H(OCH_2CH_2)_nOH$ may be used to represent polyethylene glycol, where n is a number m in the previous formula + 1.

See Table I for the average molecular weights of typical polyethylene glycols. Note that the number that follows PEG indicates the average molecular weight of the polymer.

5 Structural Formula



6 Functional Category

Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

Table I: Structural formula and molecular weight of typical polyethylene glycol polymers.

Grade	m	Average molecular weight
PEG 200	4.2	190–210
PEG 300	6.4	285–315
PEG 400	8.7	380–420
PEG 540 (blend)	—	500–600
PEG 600	13.2	570–613
PEG 900	15.3	855–900
PEG 1000	22.3	950–1 050
PEG 1450	32.5	1 300–1 600
PEG 1540	28.0–36.0	1 300–1 600
PEG 2000	40.0–50.0	1 800–2 200
PEG 3000	60.0–75.0	2 700–3 300
PEG 3350	75.7	3 000–3 700
PEG 4000	69.0–84.0	3 000–4 800
PEG 4600	104.1	4 400–4 800
PEG 8000	181.4	7 000–9 000

7 Applications in Pharmaceutical Formulation or Technology

Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations, including parenteral, topical, ophthalmic, oral, and rectal preparations. Polyethylene glycol has been used experimentally in biodegradable polymeric matrices used in controlled-release systems.[1]

Polyethylene glycols are stable, hydrophilic substances that are essentially nonirritant to the skin; *see* Section 14. They do not readily penetrate the skin, although the polyethylene glycols are water-soluble and are easily removed from the skin by washing, making them useful as ointment bases.[2] Solid grades are generally employed in topical ointments, with the consistency of the base being adjusted by the addition of liquid grades of polyethylene glycol.

Mixtures of polyethylene glycols can be used as suppository bases,[3] for which they have many advantages over fats. For example, the melting point of the suppository can be made higher to withstand exposure to warmer climates; release of the drug is not dependent upon melting point; the physical stability on storage is better; and suppositories are readily miscible with rectal fluids. Polyethylene glycols have the following disadvantages: they are

chemically more reactive than fats; greater care is needed in processing to avoid inelegant contraction holes in the suppositories; the rate of release of water-soluble medications decreases with the increasing molecular weight of the polyethylene glycol; and polyethylene glycols tend to be more irritating to mucous membranes than fats.

Aqueous polyethylene glycol solutions can be used either as suspending agents or to adjust the viscosity and consistency of other suspending vehicles. When used in conjunction with other emulsifiers, polyethylene glycols can act as emulsion stabilizers.

Liquid polyethylene glycols are used as water-miscible solvents for the contents of soft gelatin capsules. However, they may cause hardening of the capsule shell by preferential absorption of moisture from gelatin in the shell.

In concentrations up to approximately 30% v/v, PEG 300 and PEG 400 have been used as the vehicle for parenteral dosage forms.

In solid-dosage formulations, higher-molecular-weight polyethylene glycols can enhance the effectiveness of tablet binders and impart plasticity to granules.[4] However, they have only limited binding action when used alone, and can prolong disintegration if present in concentrations greater than 5% w/w. When used for thermoplastic granulations,[5–7] a mixture of the powdered constituents with 10–15% w/w PEG 6000 is heated to 70–75°C. The mass becomes pastelike and forms granules if stirred while cooling. This technique is useful for the preparation of dosage forms such as lozenges when prolonged disintegration is required.

Polyethylene glycols can also be used to enhance the aqueous solubility or dissolution characteristics of poorly soluble compounds by making solid dispersions with an appropriate polyethylene glycol.[8] Animal studies have also been performed using polyethylene glycols as solvents for steroids in osmotic pumps.

In film coatings, solid grades of polyethylene glycol can be used alone for the film-coating of tablets or can be useful as hydrophilic polishing materials. Solid grades are also widely used as plasticizers in conjunction with film-forming polymers.[9] The presence of polyethylene glycols in film coats, especially of liquid grades, tends to increase their water permeability and may reduce protection against low pH in enteric-coating films. Polyethylene glycols are useful as plasticizers in microencapsulated products to avoid rupture of the coating film when the microcapsules are compressed into tablets.

Polyethylene glycol grades with molecular weights of 6000 and above can be used as lubricants, particularly for soluble tablets. The lubricant action is not as good as that of magnesium stearate, and stickiness may develop if the material becomes too warm during compression. An antiadherent effect is also exerted, again subject to the avoidance of overheating.

Polyethylene glycols have been used in the preparation of urethane hydrogels, which are used as controlled-release agents. Polyethylene glycol has also been used in insulin-loaded microparticles for the oral delivery of insulin;[10,11] it has been used in inhalation preparations to improve aerosolization;[12] polyethylene glycol nanoparticles have been used to improve the oral bioavailability of cyclosporine;[13] it has been used in self-assembled polymeric nanoparticles as a drug carrier;[14] and copolymer networks of polyethylene glycol grafted with poly(methacrylic acid) have been used as bioadhesive controlled drug delivery formulations.[15]

8 Description

The USP32–NF27 describes polyethylene glycol as being an addition polymer of ethylene oxide and water. Polyethylene glycol grades 200–600 are liquids; grades 1000 and above are solids at ambient temperatures.

Liquid grades (PEG 200–600) occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight but characteristic odor and a bitter, slightly burning taste. PEG 600 can occur as a solid at ambient temperatures.

Solid grades (PEG>1000) are white or off-white in color, and range in consistency from pastes to waxy flakes. They have a faint, sweet odor. Grades of PEG 6000 and above are available as free-flowing milled powders.

9 Pharmacopeial Specifications

See Table II. *See also* Section 18.

Table II: Pharmacopeial specifications for polyethylene glycol.

Test	JP XV	PhEur 6.0	USP32–NF27
Identification	+	+	–
Characters	–	+	–
Acidity or alkalinity	+	+	–
Appearance of solution	+[a]	+	+
Density			
1.110–1.140[b]	See Table IV	–	
Freezing point	See Table III	See Table IV	–
Viscosity	–	See Table IV	See Table V
Average molecular weight	See Table III	–	See Table V
pH (5% w/v solution)	See Table III	–	4.5–7.5
Hydroxyl value	–	See Table IV	–
Reducing substances	–	+	–
Residue on ignition	See Table III	–	⩽0.1%
Sulfated ash	–	⩽0.2%	–
Limit of ethylene glycol and diethylene glycol	⩽0.25%	⩽0.4%	⩽0.25%
Ethylene oxide	–	⩽1 ppm	⩽10 µg/g
1,4-Dioxane	–	⩽10 ppm	⩽10 µg/g
Heavy metals	–	⩽20 ppm	⩽5 µg/g
Water	⩽1.0%	⩽2.0%	–
Formaldehyde	–	⩽30 ppm	–

(a) For PEG 1500, 4000, 6000, 20000.
(b) For PEG 400.

Table III: Specifications from JP XV.

Type of PEG	Average molecular weight	Freezing point (°C)	pH (5% w/v solution)	Residue on ignition
400	380–420	4–8	4.0–7.0	⩽0.1%
1500	–	37–41	4.0–7.0	⩽0.1%
4000				
2 600–3 800	53–57	4.0–7.5	⩽0.2%	
6000				
7 300–9 300	56–61	4.5–7.5	⩽0.2%	
20000				
15 000–25 000	56–64	4.5–7.5	⩽0.2%	

10 Typical Properties

Density

1.11–1.14 g/cm^3 at 25°C for liquid PEGs;
1.15–1.21 g/cm^3 at 25°C for solid PEGs.

Flash point

182°C for PEG 200;
213°C for PEG 300;
238°C for PEG 400;
250°C for PEG 600.

Freezing point

<−65°C PEG 200 sets to a glass;
−15 to −8°C for PEG 300;
4–8°C for PEG 400;
15–25°C for PEG 600.

Melting point

37–40°C for PEG 1000;
44–48°C for PEG 1500;

Table IV: Specifications from PhEur 6.0.

Type of PEG	Density (g/cm^3)	Freezing point (°C)	Hydroxyl value	Viscosity (dynamic) [mPa s (cP)]	Viscosity (kinematic) [mm^2/s (cSt)]
300	1.120	–	340–394	80–105	71–94
400	1.120	–	264–300	105–130	94–116
600	1.080	15–25	178–197	15–20	13.9–18.5
1000	1.080	35–40	107–118	22–30	20.4–27.7
1500	1.080	42–48	70–80	34–50	31–46
3000	1.080	50–56	34–42	75–100	69–93
3350	1.080	53–57	30–38	83–120	76–110
4000	1.080	53–59	25–32	110–170	102–158
6000	1.080	55–61	16–22	200–270	185–250
8000	1.080	55–62	12–16	260–510	240–472
20000	1.080	⩾57	–	2700–3500	2500–3200
35000	1.080	⩾57	–	11000–14000	10000–13000

Table V: Specification for viscosity of polyethylene glycol of the given nominal molecular weight at 98.9°C ± 0.3°C from the USP32–NF27.

Type of PEG (nominal average molecular weight)	Viscosity (kinematic) [mm^2/s (cSt)]
200	3.9–4.8
300	5.4–6.4
400	6.8–8.0
500	8.3–9.6
600	9.9–11.3
700	11.5–13.0
800	12.5–14.5
900	15.0–17.0
1000	16.0–19.0
1100	18.0–22.0
1200	20.0–24.5
1300	22.0–27.5
1400	24–30
1450	25–32
1500	26–33
1600	28–36
1700	31–39
1800	33–42
1900	35–45
2000	38–49
2100	40–53
2200	43–56
2300	46–60
2400	49–65
2500	51–70
2600	54–74
2700	57–78
2800	60–83
2900	64–88
3000	67–93
3250	73–105
3350	76–110
3500	87–123
3750	99–140
4000	110–158
4250	123–177
4500	140–200
4750	155–228
5000	170–250
5500	206–315
6000	250–390
6500	295–480
7000	350–590
7500	405–735
8000	470–900

40–48°C for PEG 1540;
45–50°C for PEG 2000;
48–54°C for PEG 3000;
50–58°C for PEG 4000;
55–63°C for PEG 6000;
60–63°C for PEG 8000;
60–63°C for PEG 20000.

Moisture content Liquid polyethylene glycols are very hygroscopic, although hygroscopicity decreases with increasing molecular weight. Solid grades, e.g. PEG 4000 and above, are not hygroscopic. *See* Figures 1, 2, and 3.

Particle size distribution *see* Figures 4 and 5.

Refractive index

n_D^{25} = 1.459 for PEG 200;
n_D^{25} = 1.463 for PEG 300;
n_D^{25} = 1.465 for PEG 400;
n_D^{25} = 1.467 for PEG 600.

Solubility All grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols (after melting, if necessary). Aqueous solutions of higher-molecular-weight grades may form gels. Liquid polyethylene glycols are soluble in acetone, alcohols, benzene, glycerin, and glycols. Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol (95%), and methanol; they are slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil.

Surface tension Approximately 44 mN/m (44 dynes/cm) for liquid polyethylene glycols; approximately 55 mN/m (55 dynes/cm) for 10% w/v aqueous solution of solid polyethylene glycol.

Viscosity (kinematic) *see* Tables IV, V, and VI.

Table VI: Viscosity of selected polyethylene glycols at 25°C and 99°C.

Type of PEG	Viscosity [mm^2/s (cSt)]	
	25°C	99°C
PEG 200	39.9	4.4
PEG 300	68.8	5.9
PEG 400	90.0	7.4
PEG 600	131	11.0
PEG 1000 solid	19.5	–
PEG 2000 solid	47	–
PEG 4000 solid	180	–
PEG 6000 solid	580	–
PEG 20000 solid	6900	–

11 Stability and Storage Conditions

Polyethylene glycols are chemically stable in air and in solution, although grades with a molecular weight less than 2000 are hygroscopic. Polyethylene glycols do not support microbial growth, and they do not become rancid.

Polyethylene glycols and aqueous polyethylene glycol solutions can be sterilized by autoclaving, filtration, or gamma irradiation.[16]

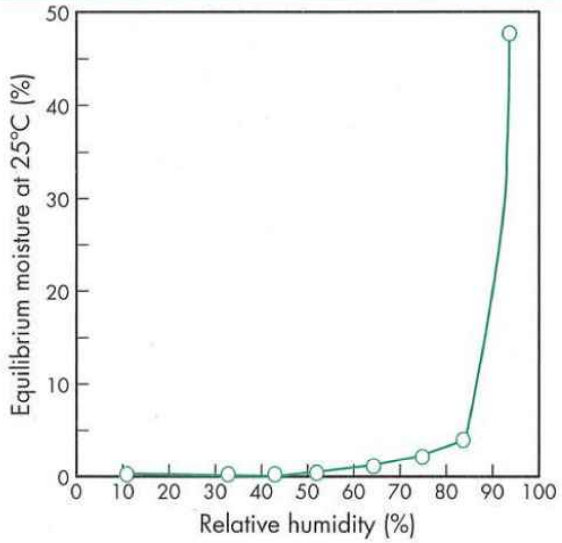


Figure 1: Equilibrium moisture content of PEG 4000 (McKesson, Lot No. B192–8209) at 25°C.

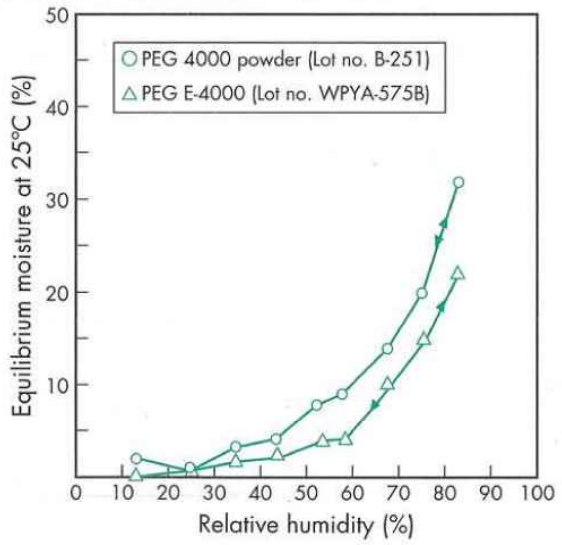


Figure 2: Equilibrium moisture content of PEG 4000 (Dow Chemical Company) and PEG E-4000 (BASF) at 25°C.

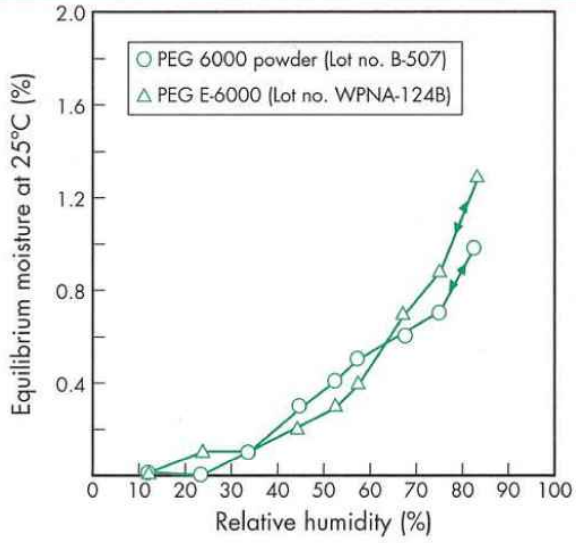


Figure 3: Equilibrium moisture content of PEG 6000 (Dow Chemical Company) and PEG E-6000 (BASF) at 25°C.

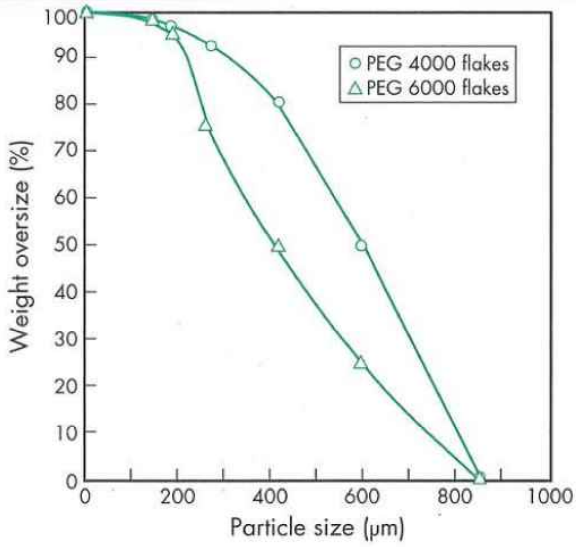


Figure 4: Particle size distribution of PEG 4000 and PEG 6000 flakes.

Sterilization of solid grades by dry heat at 150°C for 1 hour may induce oxidation, darkening, and the formation of acidic degradation products. Ideally, sterilization should be carried out in an inert atmosphere. Oxidation of polyethylene glycols may also be inhibited by the inclusion of a suitable antioxidant.

If heated tanks are used to maintain normally solid polyethylene glycols in a molten state, care must be taken to avoid contamination with iron, which can lead to discoloration. The temperature must be kept to the minimum necessary to ensure fluidity; oxidation may occur if polyethylene glycols are exposed for long periods to temperatures exceeding 50°C. However, storage under nitrogen reduces the possibility of oxidation.

Polyethylene glycols should be stored in well-closed containers in a cool, dry place. Stainless steel, aluminum, glass, or lined steel containers are preferred for the storage of liquid grades.

12 Incompatibilities

The chemical reactivity of polyethylene glycols is mainly confined to the two terminal hydroxyl groups, which can be either esterified or etherified. However, all grades can exhibit some oxidizing activity owing to the presence of peroxide impurities and secondary products formed by autoxidation.

Liquid and solid polyethylene glycol grades may be incompatible with some coloring agents.

The antibacterial activity of certain antibiotics is reduced in polyethylene glycol bases, particularly that of penicillin and bacitracin. The preservative efficacy of the parabens may also be impaired owing to binding with polyethylene glycols.

Physical effects caused by polyethylene glycol bases include softening and liquefaction in mixtures with phenol, tannic acid, and salicylic acid. Discoloration of sulfonamides and dithranol can also occur, and sorbitol may be precipitated from mixtures. Plastics, such as polyethylene, phenolformaldehyde, polyvinyl chloride, and

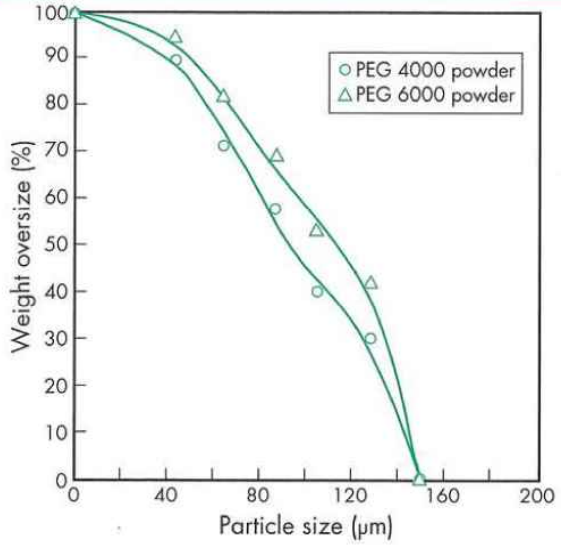


Figure 5: Particle size distribution of PEG 4000 and PEG 6000 powder.

cellulose-ester membranes (in filters) may be softened or dissolved by polyethylene glycols. Migration of polyethylene glycol can occur from tablet film coatings, leading to interaction with core components.

13 Method of Manufacture

Polyethylene glycol polymers are formed by the reaction of ethylene oxide and water under pressure in the presence of a catalyst.

14 Safety

Polyethylene glycols are widely used in a variety of pharmaceutical formulations. Generally, they are regarded as nontoxic and nonirritant materials.[17–19]

Adverse reactions to polyethylene glycols have been reported, the greatest toxicity being with glycols of low molecular weight. However, the toxicity of glycols is relatively low.

Polyethylene glycols administered topically may cause stinging, especially when applied to mucous membranes. Hypersensitivity reactions to polyethylene glycols applied topically have also been reported, including urticaria and delayed allergic reactions.[20]

The most serious adverse effects associated with polyethylene glycols are hyperosmolarity, metabolic acidosis, and renal failure following the topical use of polyethylene glycols in burn patients.[21] Topical preparations containing polyethylene glycols should therefore be used cautiously in patients with renal failure, extensive burns, or open wounds.

Oral administration of large quantities of polyethylene glycols can have a laxative effect. Therapeutically, up to 4 L of an aqueous mixture of electrolytes and high-molecular-weight polyethylene glycol is consumed by patients undergoing bowel cleansing.[22]

Liquid polyethylene glycols may be absorbed when taken orally, but the higher-molecular-weight polyethylene glycols are not significantly absorbed from the gastrointestinal tract. Absorbed polyethylene glycol is excreted largely unchanged in the urine, although polyethylene glycols of low molecular weight may be partially metabolized.

The WHO has set an estimated acceptable daily intake of polyethylene glycols at up to 10 mg/kg body-weight.[23]

In parenteral products, the maximum recommended concentration of PEG 300 is approximately 30% v/v as hemolytic effects have been observed at concentrations greater than about 40% v/v.

For animal toxicity data, *see* Table VII.[24]

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection is recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Database (dental preparations; IM and IV injections; ophthalmic preparations; oral capsules, solutions, syrups, and tablets; rectal, topical, and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Polyoxyethylene alkyl ethers; polyethylene oxide; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene stearates; suppository bases.

18 Comments

Polyethylene glycol is one of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter <1196> in the USP32–NF27, the General Chapter 5.8 in PhEur 6.0, along with the 'State of Work' document on the PhEur EDQM website, and also the General Information Chapter 8 in the JP XV.

A specification for polyethylene glycol is contained in the Food Chemicals Codex (FCC).[25]

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Table VII: Animal toxicity data (LD_{50}) for various grades of polyethylene glycol.[24]

PEG grade	LD_{50} (g/kg)								
	Guinea pig (oral)	Mouse (IP)	Mouse (IV)	Mouse (oral)	Rabbit (oral)	Rabbit (IV)	Rat (IP)	Rat (IV)	Rat (oral)
PEG 200	–	7.5	–	34	19.9	–	–	–	28.0
PEG 300	19.6	–	–	–	17.3	–	–	–	27.5
PEG 400	15.7	10.0	8.6	28.9	26.8	–	9.7	7.3	–
PEG 600	–	–	–	47	–	–	–	–	38.1
PEG 1000	–	20	–	–	–	–	15.6	–	32
PEG 1500	28.9	–	–	–	28.9	8	17.7	–	44.2
PEG 4000	50.9	–	16	–	76	–	11.6	–	50
PEG 6000	50	–	–	–	–	–	6.8	–	–

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21 Author

D Wallick.

22 Date of Revision

3 February 2009.

P

Polyethylene Oxide

1 Nonproprietary Names

USP-NF: Polyethylene Oxide

2 Synonyms

Polyox; polyoxiante; polyoxirane; polyoxyethylene.

3 Chemical Name and CAS Registry Number

Polyethylene oxide [25322-68-3]

4 Empirical Formula and Molecular Weight

See Table I.

5 Structural Formula

The USP32–NF27 describes polyethylene oxide as a nonionic homopolymer of ethylene oxide, represented by the formula $(CH_2CH_2O)_n$, where n represents the average number of oxyethylene groups. It may contain up to 3% of silicon dioxide or suitable antioxidant.

6 Functional Category

Mucoadhesive; coating agent; tablet binder; thickening agent.

7 Applications in Pharmaceutical Formulation or Technology

Polyethylene oxide can be used as a tablet binder at concentrations of 5–85%. The higher molecular weight grades provide delayed drug release via the hydrophilic matrix approach;[1,2] *see* Table I. Polyethylene oxide has also been shown to facilitate coarse extrusion for tableting[3] as well as being an aid in hot-melt extrusion.[4,5]

The relationship between swelling capacity and molecular weight is a good guide when selecting products for use in immediate- or sustained-release matrix formulations; *see* Figure 1.

Propylparaben

1 Nonproprietary Names

BP: Propyl Hydroxybenzoate
JP: Propyl Parahydroxybenzoate
PhEur: Propyl Parahydroxybenzoate
USP-NF: Propylparaben

2 Synonyms

Aseptoform P; *CoSept P*; E216; 4-hydroxybenzoic acid propyl ester; *Nipagin P*; *Nipasol M*; propagin; *Propyl Aseptoform*; propyl butex; *Propyl Chemosept*; propylis parahydroxybenzoas; propyl *p*-hydroxybenzoate; *Propyl Parasept*; *Solbrol P*; *Tegosept P*; *Uniphen P-23*.

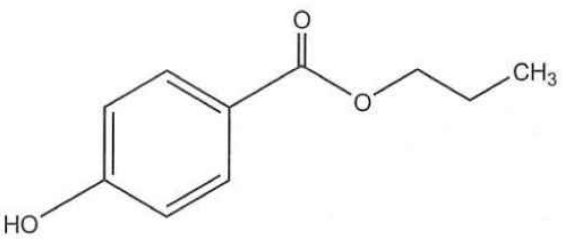
3 Chemical Name and CAS Registry Number

Propyl 4-hydroxybenzoate [94-13-3]

4 Empirical Formula and Molecular Weight

$C_{10}H_{12}O_3$ 180.20

5 Structural Formula



P

6 Functional Category

Antimicrobial preservative.

7 Applications in Pharmaceutical Formulation or Technology

Propylparaben is widely used as an antimicrobial preservative in cosmetics, food products, and pharmaceutical formulations; *see* Table I.

It may be used alone, in combination with other paraben esters, or with other antimicrobial agents. It is one of the most frequently used preservatives in cosmetics.[1]

The parabens are effective over a wide pH range and have a broad spectrum of antimicrobial activity, although they are most effective against yeasts and molds; *see* Section 10.

Owing to the poor solubility of the parabens, the paraben salts, particularly the sodium salt, are frequently used in formulations. This may cause the pH of poorly buffered formulations to become more alkaline.

Propylparaben (0.02% w/v) together with methylparaben (0.18% w/v) has been used for the preservation of various parenteral pharmaceutical formulations; *see* Section 14.

See Methylparaben for further information.

Table I: Uses of propylparaben in pharmaceutical preparations.

Use	Concentration (%)
IM, IV, SC injections	0.005–0.2
Inhalation solutions	0.015
Intradermal injections	0.02–0.26
Nasal solutions	0.017
Ophthalmic preparations	0.005–0.01
Oral solutions and suspensions	0.01–0.02
Rectal preparations	0.02–0.01
Topical preparations	0.01–0.6
Vaginal preparations	0.02–0.1

8 Description

Propylparaben occurs as a white, crystalline, odorless, and tasteless powder.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for propylparaben.

Test	JP XV	PhEur 6.0	USP32–NF27
Identification	+	+	+
Characters	–	+	–
Melting range	96.0–99.0°C	–	96.0–99.0°C
Acidity	+	+	+
Loss on drying	–	–	≤0.5%
Residue on ignition	≤0.1%	–	≤0.1%
Sulfated ash	–	≤0.1%	–
Appearance of solution	+	+	+
Heavy metals	≤20 ppm	–	–
Related substances	+	+	+
Assay	98.0–102.0%	98.0–102.0%	98.0–102.0%

10 Typical Properties

Antimicrobial activity

Propylparaben exhibits antimicrobial activity between pH 4–8. Preservative efficacy decreases with increasing pH owing to the formation of the phenolate anion. Parabens are more active against yeasts and molds than against bacteria. They are also more active against Gram-positive than against Gram-negative bacteria. The activity of the parabens increases with increasing chain length of the alkyl moiety; however, solubility decreases.

Activity may be improved by using combinations of parabens, as additive effects occur. Propylparaben has been used with methylparaben in parenteral preparations, and is used in combination with other parabens in topical and oral formulations. Activity has also been reported to be improved by the addition of other excipients; *see* Methylparaben.

Reported minimum inhibitory concentrations (MICs) for propylparaben are provided in Table III.[2]

Boiling point 295°C
Density (bulk) 0.426 g/cm^3
Density (tapped) 0.706 g/cm^3
Density(true) 1.288 g/cm^3
Dissociation constant pK_a = 8.4 at 22°C
Flash point 140°C

Table III: Minimum inhibitory concentrations (MICs) for propylparaben in aqueous solution.[2]

Microorganism	MIC (μg/mL)
Aerobacter aerogenes ATCC 8308	1000
Aspergillus niger ATCC 9642	500
Aspergillus niger ATCC 10254	200
Bacillus cereus var. *mycoides* ATCC 6462	125
Bacillus subtilis ATCC 6633	500
Candida albicans ATCC 10231	250
Enterobacter cloacae ATCC 23355	1000
Escherichia coli ATCC 8739	500
Escherichia coli ATCC 9637	100
Klebsiella pneumoniae ATCC 8308	500
Penicillium chrysogenum ATCC 9480	125
Penicillium digitatum ATCC 10030	63
Proteus vulgaris ATCC 13315	250
Pseudomonas aeruginosa ATCC 9027	>1000
Pseudomonas aeruginosa ATCC 15442	>1000
Pseudomonas stutzeri	500
Rhizopus nigricans ATCC 6227A	125
Saccharomyces cerevisiae ATCC 9763	125
Salmonella typhosa ATCC 6539	500
Serratia marcescens ATCC 8100	500
Staphylococcus aureus ATCC 6538P	500
Staphylococcus epidermidis ATCC 12228	500
Trichophyton mentagrophytes	65

NIR spectra *see* Figure 1.

Partition coefficients Values for different vegetable oils vary considerably and are affected by the purity of the oil; *see* Table IV.

Table IV: Partition coefficients for propylparaben in vegetable oil and water.[3]

Solvent	Partition coefficient oil : water
Corn oil	58.0
Mineral oil	0.5
Peanut oil	51.8
Soybean oil	65.9

Refractive index $n_D^{14} = 1.5049$

Solubility *see* Table V.

Table V: Solubility of propylparaben in various solvents.[2]

Solvent	Solubility at 20°C unless otherwise stated
Acetone	Freely soluble
Ethanol (95%)	1 in 1.1
Ethanol (50%)	1 in 5.6
Ether	Freely soluble
Glycerin	1 in 250
Mineral oil	1 in 3330
Peanut oil	1 in 70
Propylene glycol	1 in 3.9
Propylene glycol (50%)	1 in 110
Water	1 in 4350 at 15°C
	1 in 2500
	1 in 225 at 80°C

11 Stability and Storage Conditions

Aqueous propylparaben solutions at pH 3–6 can be sterilized by autoclaving, without decomposition.[4] At pH 3–6, aqueous solutions are stable (less than 10% decomposition) for up to about 4 years at room temperature, while solutions at pH 8 or above are subject to rapid hydrolysis (10% or more after about 60 days at room temperature).[5]

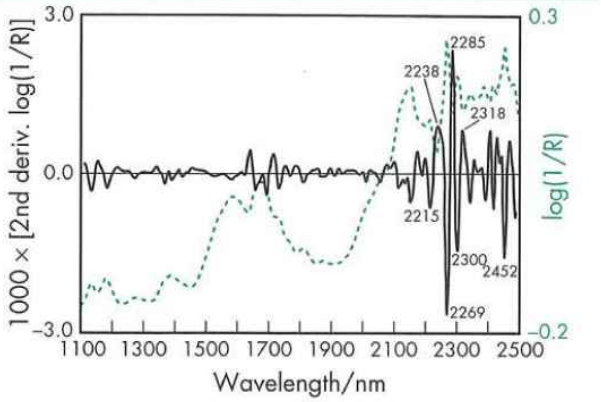


Figure 1: Near-infrared spectrum of propylparaben measured by reflectance.

See Table VI, for the predicted rate constants and half-lives at 25°C for propylparaben.[5]

Propylparaben should be stored in a well-closed container in a cool, dry place.

Table VI: Predicted rate constants and half-lives at 25°C for propylparaben dissolved in hydrochloric acid solution.

Initial pH of solution	Rate constant $k \pm \sigma^{(a)}$ (h^{-1})	Half-life $t_{1/2} \pm \sigma^{(a)}$ (day)
1	$(1.255 \pm 0.042) \times 10^{-4}$	230 ± 7.6
2	$(1.083 \pm 0.081) \times 10^{-5}$	2670 ± 200
3	$(8.41 \pm 0.96) \times 10^{-7}$	34 300 ± 3900
4	$(2.23 \pm 0.37) \times 10^{-7}$	130 000 ± 22 000

(a) σ indicates the standard error.

The predicted amount of propylparaben remaining after autoclaving is given in Table VII.[5]

Table VII: Predicted amount of propylparaben dissolved in hydrochloric acid, after autoclaving.

Initial pH of solution	Rate constant $k \pm \sigma^{(a)}$ (h^{-1})	Predicted residual amount after sterilization (%)
1	$(4.42 \pm 0.10) \times 10^{-1}$	86.30 ± 0.30
2	$(4.67 \pm 0.19) \times 10^{-2}$	98.46 ± 0.06
3	$(2.96 \pm 0.24) \times 10^{-3}$	99.90 ± 0.01
4	$(7.8 \pm 1.1) \times 10^{-4}$	99.97 ± 0.004

(a) σ indicates the standard error.

12 Incompatibilities

The antimicrobial activity of propylparaben is reduced considerably in the presence of nonionic surfactants as a result of micellization.[6] Absorption of propylparaben by plastics has been reported, with the amount absorbed dependent upon the type of plastic and the vehicle.[7] Magnesium aluminum silicate, magnesium trisilicate, yellow iron oxide, and ultramarine blue have also been reported to absorb propylparaben, thereby reducing preservative efficacy.[8,9]

Propylparaben is discolored in the presence of iron and is subject to hydrolysis by weak alkalis and strong acids.

See also Methylparaben.

13 Method of Manufacture

Propylparaben is prepared by the esterification of *p*-hydroxybenzoic acid with *n*-propanol.

14 Safety

Propylparaben and other parabens are widely used as antimicrobial preservatives in cosmetics, food products, and oral and topical pharmaceutical formulations.

Propylparaben and methylparaben have been used as preservatives in injections and ophthalmic preparations; however, they are now generally regarded as being unsuitable for these types of formulations owing to the irritant potential of the parabens.

Systemically, no adverse reactions to parabens have been reported, although they have been associated with hypersensitivity reactions. The WHO has set an estimated acceptable total daily intake for methyl, ethyl, and propyl parabens at up to 10 mg/kg body-weight.[10]

LD_{50} (mouse, IP): 0.2 g/kg[11]
LD_{50} (mouse, oral): 6.33 g/kg
LD_{50} (mouse, SC): 1.65 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Propylparaben may be irritant to the skin, eyes, and mucous membranes, and should be handled in a well-ventilated environment. Eye protection, gloves, and a dust mask or respirator are recommended.

16 Regulatory Status

Propylparaben and methylparaben are affirmed GRAS direct food substances in the USA at levels up to 0.1%. All esters except the benzyl ester are allowed for injection in Japan.

In cosmetics, the EU and Brazil allow use of each paraben at 0.4%, but the total of all parabens may not exceed 0.8%. The upper limit in Japan is 1.0%.

Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Database (IM, IV, and SC injections; inhalations; ophthalmic preparations; oral capsules, solutions, suspensions, and tablets; otic, rectal, topical, and vaginal preparations). Included in parenteral and nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

P

17 Related Substances

Butylparaben; ethylparaben; methylparaben; propylparaben potassium; propylparaben sodium.

Propylparaben potassium

Empirical formula $C_{10}H_{11}KO_3$
Molecular weight 218.30
CAS number [84930-16-5]
Synonyms Potassium propyl hydroxybenzoate; propyl 4-hydroxybenzoate potassium salt.

18 Comments

Propylparaben is one of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter <1196> in the USP32-NF27, the General Chapter 5.8 in PhEur 6.0, along with the 'State of Work' document on the PhEur EDQM website, and also the General Information Chapter 8 in the JP XV.

A specification for propylparaben is contained in the Food Chemicals Codex (FCC)[12].

The EINECS number for propylparaben is 202-307-7. The PubChem Compound ID (CID) for propylparaben is 7175.

See Methylparaben for further information and references.

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21 Author

S Haley.

22 Date of Revision

3 February 2009.

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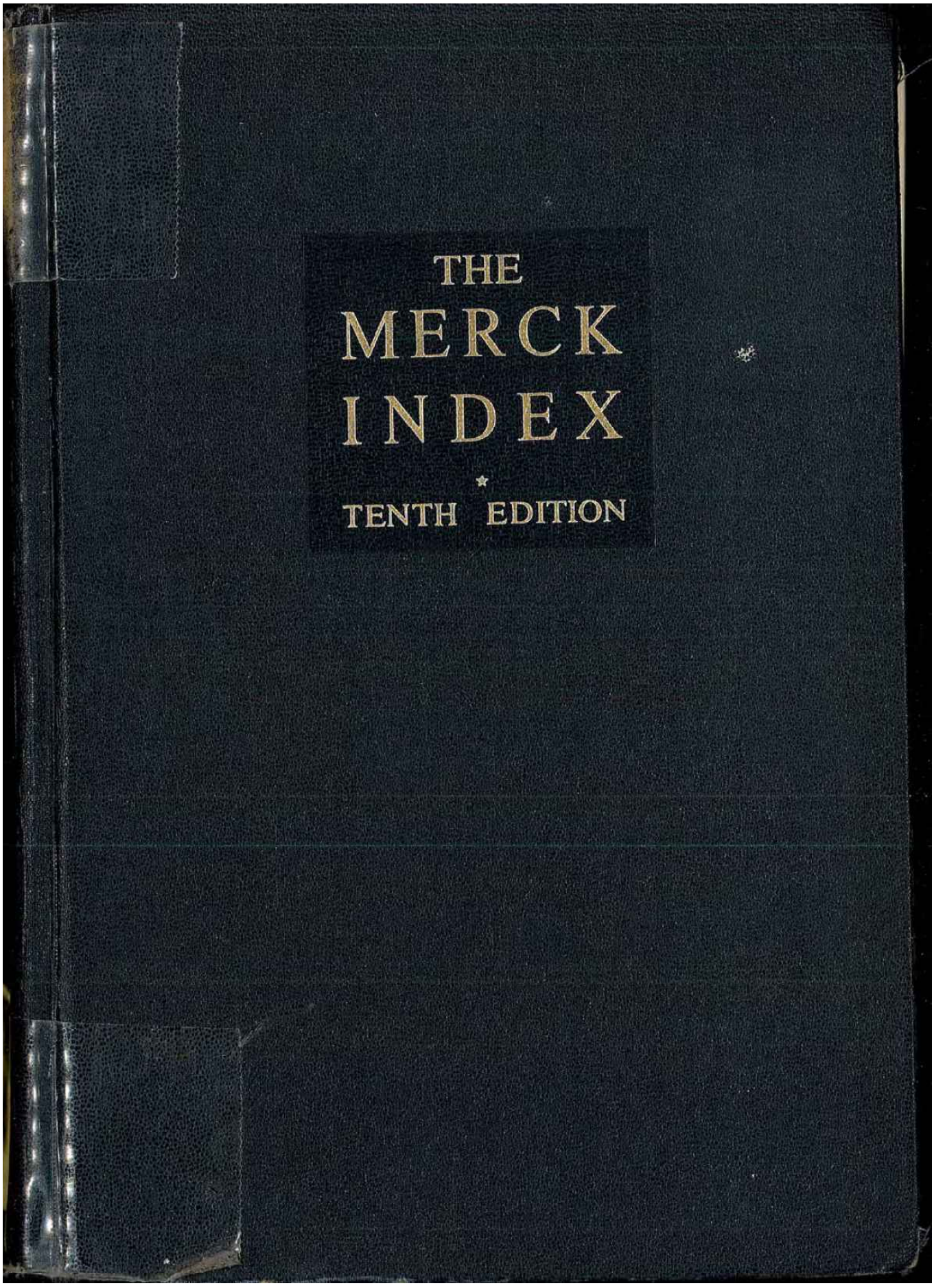
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+2 +4 46 Pd 106.42 -18-18-0	+1 47 Ag 107.868 -18-18-1	+2 48 Cd 112.41 -18-18-2	+3 49 In 114.82 -18-18-3	+2 +4 50 Sn 118.69 -18-18-4	±3 +5 51 Sb 121.75 -18-18-5	+4 +6 −2 52 Te 127.60 -18-18-6	±1 +5 +7 53 I 126.9045 -18-18-7	0 54 Xe 131.29 -18-18-8
+2 +4 78 Pt 195.08 -32-16-2	+1 +3 79 Au 196.9665 -32-18-1	+1 +2 80 Hg 200.59 -32-18-2	+1 +3 81 Tl 204.383 -32-18-3	+2 +4 82 Pb 207.2 -32-18-4	+3 +5 83 Bi 208.9804 -32-18-5	+2 +4 84 Po (209) -32-18-6	±1 +5 +7 85 At (210) -32-18-7	0 86 Rn (222) -32-18-8

Noble Gases

+3 65 Tb 158.9254 -27-8-2	+3 66 Dy 162.50 -28-8-2	+3 67 Ho 164.9304 -29-8-2	+3 68 Er 167.26 -30-8-2	+3 69 Tm 168.9342 -31-8-2	+2 +3 70 Yb 173.04 -32-8-2	+3 71 Lu 174.967 -32-9-2
+3 +4 97 Bk (247) -27-8-2	+3 98 Cf (251) -28-8-2	+3 99 Es (252) -29-8-2	+3 100 Fm (257) -30-8-2	+2 +3 101 Md (258) -31-8-2	+2 +3 102 No (259) -32-8-2	+3 103 Lr (260) -32-9-2

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Published by
MERCK & CO., INC.
RAHWAY, N.J., U.S.A.

1983

Merck & Co., Inc.
Rahway, New Jersey, U.S.A.

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1st Edition – 1889
2nd Edition – 1896
3rd Edition – 1907
4th Edition – 1930
5th Edition – 1940
6th Edition – 1952
7th Edition – 1960
8th Edition – 1968
9th Edition – 1976
10th Edition – 1983

Library of Congress Catalog
Card Number 83-61075
ISBN Number 911910-27-1

Printed in the U.S.A.

Isotonic Solutions

The following table provides data for adjusting aqueous solutions of chemical substances, by both the freezing point depression method and the sodium chloride equivalent method, so that they will be isosmotic with normal saline solution and presumably, therefore, isotonic with blood and tears. The freezing point depression values have been determined experimentally and published by E. R. Hammarlund, K. Pedersen-Bjergaard, J. F. Deming, W. E. Fassett, T. S. Fuller, M. Lord, C. Sapp and G. L. Van Pevenage. The sodium chloride equivalent values have been calculated from these data. Because of a general interest in the colligative properties of some medicinal solutions, values are included for certain substances which are not used necessarily as isotonic solutions.

The values first listed for each chemical substance are sodium chloride equivalents. The second values, in *italic*, are freezing point depression values in degree Centigrade. The percentage concentration (w/v) at isotonicity (isosmotic) is given in bold face in the last column.

To prepare an isotonic solution by the method of sodium chloride equivalents, the osmotic equivalent of each ingredient is calculated by multiplying the number of grams of each ingredient present in the preparation by its sodium chloride equivalent from the table at (or nearest to) the proper concentration. The resulting osmotic equivalents are added together (if more than one ingredient) and the total is subtracted from the number of grams of sodium chloride required to make that specified volume of normal saline solution (0.9%), i.e., 0.27 g for 30 ml, 0.54 g for 60 ml, or 0.90 g NaCl for 100 ml of desired solution. The difference is the grams of sodium chloride which must be added to that specific volume of preparation to make it approximately isotonic (actually isosmotic) with blood or tears.

If the value of the osmotic equivalent is found to be larger than the weight of sodium chloride required to prepare that volume of normal saline solution (i.e., the difference in the subtraction step is less than zero), then the solution is already hypertonic and cannot be adjusted to isotonicity without altering concentrations of the given ingredients.

If the solution can be made isotonic and one desires to use a different adjusting chemical, such as dextrose or boric acid rather than sodium chloride, one merely divides the grams of sodium chloride previously found necessary to add by the sodium chloride equivalent of the desired chemical, i.e., 0.16 for dextrose (anhyd) or 0.47 for boric acid (from the table), and one obtains directly the grams of other substance to use for isotonicity adjustment instead of sodium chloride. One should refer to any customary pharmacy text for further explanation and examples if necessary.

Sodium Chloride Equivalents and Freezing Point Depressions (°C)
for Certain Concentrations (w/v) of Solution

Chemical	Concentration of Solution, NaCl Equivalents						
	½%	1%	2%	3%	5%	At Isosmotic Concentration	
Acetazolamide sodium	0.24 *0.068°*	0.23 *0.135°*	0.23 *0.271°*	0.23 *0.406°*	– –	0.23 *0.52°*	**3.85%** **3.85%**
Acetrizoate methylglucamine	0.09 *0.024°*	0.08 *0.047°*	0.08 *0.093°*	0.08 *0.137°*	0.08 *0.222°*	0.07 *0.52°*	**12.12%** **12.12%**
Acetrizoate sodium	0.10 *0.027°*	0.10 *0.055°*	0.10 *0.109°*	0.10 *0.163°*	0.10 *0.273°*	0.09 *0.52°*	**9.64%** **9.64%**
Acetylcysteine	0.20 *0.055°*	0.20 *0.113°*	0.20 *0.227°*	0.20 *0.341°*	– –	0.20 *0.52°*	**4.58%** **4.58%**
Acetylsulfanilamide sodium	0.24 *0.066°*	0.23 *0.133°*	0.23 *0.268°*	0.23 *0.406°*	– –	0.23 *0.52°*	**3.85%** **3.85%**
Acriflavine	0.10 *0.025°*	0.10 *0.050°*	0.09 *0.101°*	0.09 *0.151°*	– –	– –	
Adenosine phosphate	0.50 *0.140°*	0.41 *0.234°*	– –	– –	– –	– –	
Adiphenine hydrochloride	0.28 *0.083°*	0.22 *0.126°*	0.17 *0.194°*	0.15 *0.250°*	0.12 *0.346°*	– –	
Adrenalone hydrochloride	0.30 *0.086°*	0.27 *0.154°*	0.24 *0.275°*	0.22 *0.387°*	– –	0.21 *0.52°*	**4.24%** **4.24%**
Alcohol	0.65 *0.188°*	0.65 *0.375°*	– –	– –	– –	0.65 *0.52°*	**1.39%** **1.39%**
Alcohol, dehydrated	0.70 *0.203°*	0.70 *0.406°*	– –	– –	– –	0.70 *0.52°*	**1.28%** **1.28%**
Alphaprodine hydrochloride	0.19 *0.053°*	0.19 *0.105°*	0.18 *0.212°*	0.18 *0.315°*	– –	0.18 *0.52°*	**4.98%** **4.98%**
Alum, potassium	0.20 *0.054°*	0.18 *0.100°*	0.16 *0.185°*	0.15 *0.265°*	0.15 *0.418°*	0.14 *0.52°*	**6.35%** **6.35%**

Isotonic Solutions (Continued)

Chemical	Concentration of Solution, NaCl Equivalents					At Isosmotic Concentration	
	½%	1%	2%	3%	5%		
Amantadine hydrochloride	0.31 *0.090°*	0.31 *0.180°*	0.31 *0.354°*	– –	– –	0.31 *0.52°*	2.95% 2.95%
Amidoxyl benzoate	0.20 *0.059°*	0.20 *0.118°*	0.20 *0.236°*	0.20 *0.353°*	– –	0.20 *0.52°*	4.42% 4.42%
Amikacin	0.06 *0.016°*	0.05 *0.031°*	0.05 *0.062°*	0.05 *0.091°*	0.05 *0.153°*	– –	
Aminacrine hydrochloride	0.20 *0.052°*	0.17 *0.097°*	– –	– –	– –	– –	
Aminoacetic acid	0.42 *0.119°*	0.41 *0.235°*	0.41 *0.470°*	– –	– –	0.41 *0.52°*	2.20% 2.20%
Aminocaproic acid	0.26 *0.075°*	0.26 *0.148°*	0.26 *0.297°*	0.26 *0.444°*	– –	– –	
p-Aminohippuric acid	0.13 *0.035°*	0.13 *0.075°*	– –	– –	– –	– –	
Aminophylline	0.18 *0.056°*	0.17 *0.100°*	– –	– –	– –	– –	
p-Aminosalicylate sodium	0.30 *0.086°*	0.29 *0.169°*	0.29 *0.326°*	0.28 *0.479°*	– –	0.27 *0.52°*	3.27% 3.27%
Amitriptyline hydrochloride	0.24 *0.070°*	0.18 *0.100°*	0.11 *0.125°*	0.08 *0.147°*	0.06 *0.177°*	– –	
Ammonium carbonate	0.70 *0.202°*	0.70 *0.405°*	– –	– –	– –	0.70 *0.52°*	1.29% 1.29%
Ammonium chloride	1.16 *0.331°*	– –	– –	– –	– –	1.12 *0.52°*	0.8% 0.8%
Ammonium lactate	0.33 *0.093°*	0.33 *0.185°*	0.33 *0.370°*	– –	– –	0.33 *0.52°*	2.76% 2.76%
Ammonium nitrate	0.69 *0.200°*	0.69 *0.400°*	– –	– –	– –	0.69 *0.52°*	1.30% 1.30%
Ammonium phosphate, dibasic	0.58 *0.165°*	0.55 *0.315°*	– –	– –	– –	0.51 *0.52°*	1.76% 1.76%
Ammonium sulfate	0.55 *0.158°*	0.55 *0.315°*	– –	– –	– –	0.54 *0.52°*	1.68% 1.68%
Amobarbital sodium	0.26 *0.074°*	0.25 *0.144°*	0.25 *0.293°*	0.25 *0.440°*	– –	0.25 *0.52°*	3.6% 3.6%
Amphetamine phosphate	0.38 *0.114°*	0.34 *0.196°*	0.30 *0.338°*	0.27 *0.466°*	– –	0.26 *0.52°*	3.47% 3.47%
Amphetamine sulfate	0.22 *0.066°*	0.22 *0.128°*	0.22 *0.251°*	0.21 *0.371°*	– –	0.21 *0.52°*	4.23% 4.23%
Ampicillin sodium	0.16 *0.045°*	0.16 *0.090°*	0.16 *0.181°*	0.16 *0.272°*	0.16 *0.451°*	0.16 *0.52°*	5.78% 5.78%
Amprotropine phosphate	0.19 *0.058°*	0.18 *0.106°*	0.17 *0.196°*	0.16 *0.281°*	0.15 *0.445°*	– –	
Amydricaine hydrochloride	0.28 *0.080°*	0.24 *0.136°*	0.20 *0.231°*	0.18 *0.316°*	0.16 *0.467°*	0.16 *0.52°*	5.74% 5.74%
Amydricaine nitrate	0.20 *0.058°*	0.19 *0.106°*	0.18 *0.199°*	0.17 *0.289°*	0.16 *0.461°*	0.16 *0.52°*	5.68% 5.68%

Chemical	Concentration of Solution, NaCl Equivalents					At Isosmotic Concentration	
	½%	1%	2%	3%	5%		
Anileridine hydrochloride	0.19 *0.052°*	0.19 *0.104°*	0.19 *0.212°*	0.18 *0.316°*	0.18 *0.509°*	0.18 *0.52°*	**5.13%** **5.13%**
Antazoline hydrochloride	0.25 *0.073°*	0.23 *0.131°*	0.21 *0.245°*	– –	– –	– –	
Antazoline phosphate	0.20 *0.062°*	0.20 *0.112°*	0.18 *0.204°*	0.17 *0.291°*	0.15 *0.445°*	– –	
Antimony potassium tartrate	0.22 *0.065°*	0.18 *0.106°*	0.15 *0.174°*	0.13 *0.232°*	0.10 *0.331°*	– –	
Antipyrine	0.18 *0.050°*	0.17 *0.094°*	0.16 *0.174°*	0.14 *0.250°*	0.14 *0.394°*	0.13 *0.52°*	**6.81%** **6.81%**
Apomorphine hydrochloride	0.14 *0.041°*	0.14 *0.080°*	0.14 *0.155°*	– –	– –	– –	
Arecoline hydrobromide	0.30 *0.084°*	0.27 *0.155°*	0.25 *0.286°*	0.24 *0.413°*	– –	0.23 *0.52°*	**3.88%** **3.88%**
Arginine glutamate	0.17 *0.048°*	0.17 *0.097°*	0.17 *0.195°*	0.17 *0.292°*	0.17 *0.487°*	0.17 *0.52°*	**5.37%** **5.37%**
Arsenic trioxide	0.30 *0.085°*	0.30 *0.169°*	– –	– –	– –	– –	
Ascorbic acid	0.20 *0.053°*	0.18 *0.105°*	0.18 *0.209°*	0.18 *0.311°*	0.18 *0.516°*	0.18 *0.52°*	**5.94%** **5.94%**
Atropine methylnitrate	0.20 *0.055°*	0.18 *0.101°*	0.16 *0.185°*	0.15 *0.264°*	0.14 *0.412°*	0.14 *0.52°*	**6.52%** **6.52%**
Atropine sulfate	0.14 *0.039°*	0.13 *0.073°*	0.12 *0.136°*	0.11 *0.196°*	0.11 *0.311°*	0.10 *0.52°*	**8.85%** **8.85%**
Aurothioglucose	0.03 *0.007°*	0.03 *0.014°*	0.03 *0.028°*	0.03 *0.044°*	0.03 *0.073°*	– –	
Bacitracin	0.06 *0.016°*	0.05 *0.028°*	0.05 *0.052°*	0.04 *0.075°*	0.04 *0.120°*	– –	
Barbital sodium	0.32 *0.087°*	0.30 *0.171°*	0.29 *0.336°*	0.29 *0.500°*	– –	0.29 *0.52°*	**3.12%** **3.12%**
Benoxinate hydrochloride	0.20 *0.061°*	0.18 *0.104°*	0.15 *0.175°*	0.14 *0.239°*	– –	– –	
Benzalkonium chloride	0.18 0.048°	0.16 *0.091°*	0.15 *0.170°*	0.14 *0.245°*	0.13 *0.388°*	– –	
Benzethonium chloride	0.08 *0.022°*	0.05 *0.028°*	0.03 *0.037°*	0.02 *0.043°*	0.02 *0.051°*	– –	
Benzpyrinium bromide	0.20 *0.061°*	0.20 *0.114°*	0.19 *0.213°*	0.18 *0.309°*	0.17 *0.483°*	– –	
Benzquinamide hydrochloride	0.14 *0.041°*	0.14 *0.079°*	0.13 *0.150°*	0.12 *0.216°*	– –	– –	
Benztropine mesylate	0.26 *0.073°*	0.21 *0.115°*	0.15 *0.170°*	0.12 *0.203°*	0.09 *0.242°*	– –	
Benzyl alcohol	0.18 *0.049°*	0.17 *0.095°*	0.16 *0.182°*	0.15 *0.266°*	– –	– –	
Benzylpenicillin potassium	0.18 *0.052°*	0.18 *0.101°*	0.17 *0.197°*	0.17 *0.290°*	0.16 *0.474°*	0.16 *0.52°*	**5.48%** **5.48%**

Isotonic Solutions (Continued)

Chemical	Concentration of Solution. NaCl Equivalents					At Isosmotic Concentration	
	½%	1%	2%	3%	5%		
Benzylpenicillin sodium	0.18 *0.052°*	0.18 *0.100°*	0.17 *0.190°*	0.16 *0.280°*	0.16 *0.451°*	— —	
Betazole hydrochloride	0.54 *0.158°*	0.51 *0.294°*	— —	— —	— —	0.47 *0.52°*	**1.91%** **1.91%**
Bethanechol chloride	0.50 *0.140°*	0.39 *0.225°*	0.32 *0.368°*	0.30 *0.512°*	— —	0.30 *0.52°*	**3.05%** **3.05%**
Bismuth potassium tartrate	0.10 *0.033°*	0.09 *0.051°*	0.07 *0.080°*	0.06 *0.103°*	0.05 *0.142°*	— —	
Bismuth sodium tartrate	0.14 *0.041°*	0.13 *0.075°*	0.13 *0.139°*	0.12 *0.199°*	0.11 *0.312°*	0.10 *0.52°*	**8.91%** **8.91%**
Boric acid	0.52 *0.146°*	0.50 *0.283°*	— —	— —	— —	0.47 *0.52°*	**1.9%** **1.9%**
Bretylium tosylate	0.16 *0.043°*	0.14 *0.081°*	0.13 *0.148°*	0.12 *0.208°*	0.11 *0.327°*	— —	
Bromodiphenhydramine hydrochloride	0.20 *0.067°*	0.17 *0.106°*	0.14 *0.166°*	0.10 *0.186°*	0.07 *0.209°*	— —	
Brompheniramine maleate	0.10 *0.026°*	0.09 *0.050°*	0.08 *0.084°*	— —	— —	— —	
Bupivacaine hydrochloride	0.17 *0.048°*	0.17 *0.096°*	0.17 *0.193°*	0.17 *0.290°*	0.17 *0.484°*	0.17 *0.52°*	**5.38%** **5.38%**
Butabarbital sodium	0.27 *0.078°*	0.27 *0.155°*	0.27 *0.313°*	0.27 *0.470°*	— —	0.27 *0.52°*	**3.33%** **3.33%**
Butacaine sulfate	0.26 *0.073°*	0.20 *0.114°*	0.16 *0.175°*	0.13 *0.223°*	0.10 *0.304°*	— —	
Butethamine formate	0.28 *0.077°*	0.26 *0.148°*	0.24 *0.266°*	0.21 *0.370°*	— —	0.20 *0.52°*	**4.56%** **4.56%**
Butethamine hydrochloride	0.28 *0.079°*	0.25 *0.141°*	0.22 *0.251°*	— —	— —	— —	
Caffeine	0.08 *0.025°*	0.08 *0.048°*	— —	— —	— —	— —	
Calcium aminosalicylate	0.30 *0.091°*	0.27 *0.154°*	0.23 *0.264°*	0.21 *0.361°*	— —	— —	
Calcium chloride ($2H_2O$)	0.50 *0.145°*	0.51 *0.298°*	— —	— —	— —	0.53 *0.52°*	**1.70%** **1.70%**
Calcium chloride ($6H_2O$)	0.34 *0.097°*	0.35 *0.200°*	0.36 *0.414°*	— —	— —	0.36 *0.52°*	**2.5%** **2.5%**
Calcium chloride, anhydrous	0.66 *0.191°*	0.68 *0.395°*	— —	— —	— —	0.69 *0.52°*	**1.3%** **1.3%**
Calcium disodium edetate	0.21 *0.061°*	0.21 *0.120°*	0.21 *0.240°*	0.20 *0.357°*	— —	0.20 *0.52°*	**4.50%** **4.50%**
Calcium gluconate	0.18 *0.050°*	0.16 *0.091°*	0.15 *0.167°*	0.14 *0.237°*	— —	— —	
Calcium lactate	0.26 *0.073°*	0.23 *0.135°*	0.22 *0.253°*	0.21 *0.370°*	— —	0.20 *0.52°*	**4.5%** **4.5%**
Calcium lactobionate	0.08 *0.022°*	0.08 *0.043°*	0.08 *0.085°*	0.07 *0.126°*	0.07 *0.197°*	— —	

Isotonic Solutions (Continued)

Chemical	Concentration of Solution, NaCl Equivalents						
	½%	1%	2%	3%	5%	At Isosmotic Concentration	
Calcium levulinate	0.30 *0.080°*	0.27 *0.155°*	0.26 *0.304°*	0.25 *0.442°*	– –	– –	
Calcium pantothenate	0.20 *0.055°*	0.19 *0.105°*	0.18 *0.201°*	0.17 *0.293°*	0.16 *0.470°*	0.16 *0.52°*	**5.6%** **5.6%**
Capreomycin sulfate	0.04 *0.011°*	0.04 *0.020°*	0.04 *0.042°*	0.04 *0.063°*	0.04 *0.106°*	– –	
Carbachol	0.40 *0.108°*	0.36 *0.203°*	0.34 *0.383°*	– –	– –	0.32 *0.52°*	**2.82%** **2.82%**
Carbazochrome salicylate	0.38 *0.106°*	0.36 *0.210°*	0.36 *0.410°*	– –	– –	0.35 *0.52°*	**2.57%** **2.57%**
Carbenicillin disodium	0.20 *0.059°*	0.20 *0.118°*	0.20 *0.236°*	0.20 *0.355°*	– –	0.20 *0.52°*	**4.40%** **4.40%**
Cefamandole nafate	0.16 *0.045°*	0.14 *0.079°*	0.12 *0.137°*	0.11 *0.187°*	0.10 *0.290°*	– –	
Cefazolin sodium	0.14 *0.042°*	0.13 *0.074°*	0.12 *0.132°*	0.11 *0.190°*	0.11 *0.303°*	– –	
Cefoxitin sodium	0.18 *0.050°*	0.16 *0.092°*	0.15 *0.166°*	0.14 *0.238°*	0.13 *0.384°*	– –	
Cephaloridine	0.09 *0.023°*	0.07 *0.041°*	0.06 *0.074°*	0.06 *0.106°*	0.05 *0.145°*	– –	
Cephalothin sodium	0.18 *0.050°*	0.17 *0.095°*	0.16 *0.179°*	0.15 *0.259°*	0.14 *0.400°*	0.13 *0.52°*	**6.80%** **6.80%**
Cephapirin sodium	0.14 *0.038°*	0.13 *0.075°*	0.13 *0.149°*	0.13 *0.222°*	0.12 *0.361°*	0.11 *0.52°*	**7.80%** **7.80%**
Cetrimonium bromide	0.10 *0.030°*	0.09 *0.051°*	0.09 *0.105°*	0.09 *0.148°*	0.08 *0.233°*	– –	
Chiniofon	0.14 *0.039°*	0.13 *0.073°*	0.12 *0.139°*	0.11 *0.200°*	– –	– –	
Chloramine-T	0.24 *0.064°*	0.23 *0.129°*	0.22 *0.255°*	0.22 *0.383°*	– –	0.22 *0.52°*	**4.1%** **4.1%**
Chloramphenicol sodium succinate	0.14 *0.038°*	0.14 *0.078°*	0.14 *0.154°*	0.13 *0.230°*	0.13 *0.382°*	0.13 *0.52°*	**6.83%** **6.83%**
Chlorcyclizine hydrochloride	0.24 *0.068°*	0.17 *0.095°*	0.12 *0.132°*	0.09 *0.161°*	0.07 *0.205°*	– –	
Chlordiazepoxide hydrochloride	0.24 *0.068°*	0.22 *0.125°*	0.19 *0.220°*	0.18 *0.315°*	0.17 *0.487°*	0.16 *0.52°*	**5.50%** **5.50%**
Chlorobutanol, hydrated	0.24 *0.071°*	– –	– –	– –	– –	– –	
Chlorophyll	0.14 *0.037°*	0.10 *0.056°*	0.08 *0.087°*	0.06 *0.113°*	0.05 *0.154°*	– –	
2-Chloroprocaine hydrochloride	0.20 *0.054°*	0.20 *0.108°*	0.18 *0.210°*	– –	– –	– –	
Chloroquine phosphate	0.14 *0.039°*	0.14 *0.082°*	0.14 *0.162°*	0.14 *0.242°*	0.13 *0.379°*	0.13 *0.52°*	**7.15%** **7.15%**
Chloroquine sulfate	0.10 *0.028°*	0.09 *0.050°*	0.08 *0.090°*	0.07 *0.127°*	0.07 *0.195°*	– –	

Isotonic Solutions (Continued)

Chemical	Concentration of Solution, NaCl Equivalents						
	½%	1%	2%	3%	5%	At Isosmotic Concentration	
Chlorpheniramine maleate	0.18 *0.049°*	0.17 *0.087°*	0.14 *0.160°*	0.12 *0.223°*	0.09 *0.268°*	— —	
Chlorpromazine hydrochloride	0.18 *0.052°*	0.10 *0.058°*	0.06 *0.069°*	0.05 *0.078°*	0.03 *0.100°*	— —	
Chlortetracycline hydrochloride	0.10 *0.030°*	0.10 *0.061°*	0.10 *0.121°*	— —	— —	— —	
Chlortetracycline sulfate	0.16 *0.047°*	0.13 *0.077°*	0.11 *0.127°*	0.10 *0.170°*	— —	— —	
Citric acid	0.18 *0.050°*	0.18 *0.098°*	0.17 *0.193°*	0.17 *0.287°*	0.16 *0.472°*	0.16 *0.52°*	**5.52%** **5.52%**
Clindamycin phosphate	0.08 *0.022°*	0.08 *0.046°*	0.08 *0.095°*	0.08 *0.144°*	0.08 *0.242°*	0.08 *0.52°*	**10.73%** **10.73%**
Cocaine hydrochloride	0.16 *0.047°*	0.16 *0.091°*	0.16 *0.175°*	0.15 *0.256°*	0.14 *0.416°*	0.14 *0.52°*	**6.33%** **6.33%**
Codeine hydrochloride	0.16 *0.045°*	0.15 *0.087°*	0.15 *0.171°*	0.15 *0.253°*	— —	— —	
Codeine phosphate	0.14 *0.040°*	0.14 *0.078°*	0.13 *0.151°*	0.13 *0.223°*	0.13 *0.362°*	0.12 *0.52°*	**7.29%** **7.29%**
Colistimethate sodium	0.15 *0.045°*	0.15 *0.085°*	0.15 *0.170°*	0.15 *0.253°*	0.14 *0.411°*	0.13 *0.52°*	**6.73%** **6.73%**
Congo red	0.05 *0.015°*	0.05 *0.030°*	0.05 *0.059°*	0.05 *0.092°*	0.05 *0.151°*	— —	
Cupric sulfate	0.20 *0.054°*	0.18 *0.098°*	0.16 *0.179°*	0.15 *0.254°*	0.14 *0.396°*	0.13 *0.52°*	**6.85%** **6.85%**
Cupric sulfate, anhydrous	0.30 *0.084°*	0.27 *0.153°*	0.25 *0.280°*	0.23 *0.397°*	— —	0.22 *0.52°*	**4.09%** **4.09%**
Cyclizine hydrochloride	0.20 *0.060°*	— —	— —	— —	— —	— —	
Cyclomethycaine sulfate	0.16 *0.046°*	0.13 *0.076°*	0.11 *0.126°*	0.10 *0.169°*	0.09 *0.245°*	— —	
Cyclopentamine hydrochloride	0.36 *0.104°*	0.36 *0.204°*	0.35 *0.392°*	— —	— —	0.34 *0.52°*	**2.68%** **2.68%**
Cyclopentolate hydrochloride	0.22 *0.061°*	0.20 *0.117°*	0.19 *0.218°*	0.18 *0.319°*	0.17 *0.499°*	0.17 *0.52°*	**5.30%** **5.30%**
Cyclophosphamide	0.10 *0.031°*	0.10 *0.061°*	0.10 *0.125°*	— —	— —	— —	
Cytarabine	0.11 *0.034°*	0.11 *0.066°*	0.11 *0.134°*	0.11 *0.198°*	0.11 *0.317°*	0.10 *0.52°*	**8.92%** **8.92%**
Decamethonium bromide	0.29 *0.084°*	0.25 *0.144°*	0.22 *0.256°*	0.20 *0.350°*	0.18 *0.520°*	0.18 *0.52°*	**5.0%** **5.0%**
Deferoxamine mesylate	0.09 *0.023°*	0.09 *0.047°*	0.09 *0.093°*	0.09 *0.142°*	0.09 *0.241°*	— —	
Demecarium bromide	0.14 *0.038°*	0.12 *0.069°*	0.10 *0.108°*	0.08 *0.139°*	0.07 *0.192°*	— —	
Dexamethasone sodium phosphate	0.18 *0.050°*	0.17 *0.095°*	0.16 *0.180°*	0.15 *0.260°*	0.14 *0.410°*	0.13 *0.52°*	**6.75%** **6.75%**

Isotonic Solutions (Continued)

Chemical	Concentration of Solution, NaCl Equivalents						
	½%	1%	2%	3%	5%	At Isosmotic Concentration	
Dexchlorpheniramine maleate	0.17 *0.048°*	0.15 *0.085°*	0.14 *0.165°*	0.13 *0.220°*	0.09 *0.265°*	– –	
Dexpanthenol	0.20 *0.053°*	0.18 *0.100°*	0.17 *0.193°*	0.17 *0.283°*	0.16 *0.468°*	0.16 *0.52°*	**5.60%** **5.60%**
Dextroamphetamine hydrochloride	0.34 *0.097°*	0.34 *0.196°*	0.34 *0.392°*	– –	– –	0.34 *0.52°*	**2.64%** **2.64%**
Dextroamphetamine phosphate	0.25 *0.072°*	0.25 *0.144°*	0.25 *0.288°*	0.25 *0.432°*	– –	0.25 *0.52°*	**3.62%** **3.62%**
Dextroamphetamine sulfate	0.24 *0.069°*	0.23 *0.134°*	0.22 *0.259°*	0.22 *0.380°*	– –	0.22 *0.52°*	**4.16%** **4.16%**
Dextrose	0.16 *0.045°*	0.16 *0.091°*	0.16 *0.184°*	0.16 *0.279°*	0.16 *0.470°*	0.16 *0.52°*	**5.51%** **5.51%**
Dextrose, anhydrous	0.18 *0.050°*	0.18 *0.100°*	0.18 *0.205°*	0.18 *0.310°*	0.18 *0.516°*	0.18 *0.52°*	**5.05%** **5.05%**
Diatrizoate sodium	0.10 *0.025°*	0.09 *0.049°*	0.09 *0.098°*	0.09 *0.149°*	0.09 *0.248°*	0.09 *0.52°*	**10.55%** **10.55%**
Dibucaine hydrochloride	0.14 *0.040°*	0.13 *0.076°*	0.12 *0.139°*	0.11 *0.188°*	0.08 *0.223°*	– –	
Dibutoline sulfate	0.18 *0.049°*	0.16 *0.093°*	0.15 *0.175°*	0.15 *0.259°*	0.14 *0.416°*	– –	
Dichlorophenarsine hydrochloride	0.55 *0.150°*	0.55 *0.310°*	– –	– –	– –	0.55 *0.52°*	**1.64%** **1.64%**
Dicloxacillin sodium (monohydrate)	0.10 *0.030°*	0.10 *0.061°*	0.10 *0.122°*	0.10 *0.182°*	– –	– –	
Dicyclomine hydrochloride	0.18 *0.052°*	0.18 *0.102°*	0.17 *0.201°*	0.17 *0.298°*	– –	– –	
Diethanolamine	0.31 *0.089°*	0.31 *0.177°*	0.31 *0.358°*	– –	– –	0.31 *0.52°*	**2.90%** **2.90%**
Diethylcarbamazine citrate	0.14 *0.042°*	0.14 *0.083°*	0.14 *0.166°*	0.14 *0.248°*	0.14 *0.415°*	0.14 *0.52°*	**6.29%** **6.29%**
Dihydrocodeinone enol acetate hydrochloride	0.15 *0.042°*	0.14 *0.080°*	0.13 *0.151°*	0.13 *0.217°*	0.12 *0.347°*	0.12 *0.52°*	**7.76%** **7.76%**
Dihydrostreptomycin sulfate	0.08 *0.017°*	0.06 *0.032°*	0.06 *0.059°*	0.05 *0.086°*	0.05 *0.137°*	0.04 *0.52°*	**21.4%** **21.4%**
Dimethindene maleate	0.13 *0.039°*	0.12 *0.070°*	0.11 *0.120°*	– –	– –	– –	
Dimethyl sulfoxide	0.42 *0.122°*	0.42 *0.245°*	0.42 *0.480°*	– –	– –	0.42 *0.52°*	**2.16%** **2.16%**
Diperodon hydrochloride	0.15 *0.045°*	0.14 *0.079°*	0.13 *0.141°*	– –	– –	– –	
Diphemanil methylsulfate	0.16 *0.047°*	0.15 *0.088°*	– –	– –	– –	– –	
Diphenhydramine hydrochloride	0.34 *0.099°*	0.27 *0.158°*	0.22 *0.256°*	0.20 *0.338°*	0.17 *0.477°*	– –	
Diphenidol hydrochloride	0.16 *0.045°*	0.16 *0.090°*	0.16 *0.180°*	– –	– –	– –	

Chemical	Concentration of Solution, NaCl Equivalents					At Isosmotic Concentration	
	½%	1%	2%	3%	5%		
Dipyrone	0.20 *0.057°*	0.19 *0.115°*	0.19 *0.223°*	0.19 *0.338°*	– –	0.19 *0.52°*	**4.65%** **4.65%**
Disodium edetate	0.24 *0.070°*	0.23 *0.132°*	0.22 *0.248°*	0.21 *0.360°*	– –	0.20 *0.52°*	**4.44%** **4.44%**
Dobutamine hydrochloride	0.20 *0.053°*	0.18 *0.101°*	0.16 *0.188°*	– –	– –	– –	
Dopamine hydrochloride	0.30 *0.085°*	0.30 *0.170°*	0.29 *0.335°*	0.29 *0.502°*	– –	0.29 *0.52°*	**3.11%** **3.11%**
Doxapram hydrochloride	0.12 *0.035°*	0.12 *0.070°*	0.12 *0.140°*	0.12 *0.210°*	– –	– –	
Doxycycline hyclate	0.12 *0.035°*	0.12 *0.072°*	0.12 *0.134°*	0.11 *0.186°*	0.09 *0.264°*	– –	
Dyclonine hydrochloride	0.26 *0.073°*	0.24 *0.135°*	0.17 *0.190°*	– –	– –	– –	
Dyphylline	0.10 *0.025°*	0.10 *0.052°*	0.09 *0.104°*	0.09 *0.155°*	0.08 *0.245°*	– –	
Echothiopate iodide	0.16 *0.045°*	0.16 *0.090°*	0.16 *0.179°*	– –	– –	– –	
Edrophonium chloride	0.32 *0.093°*	0.31 *0.175°*	0.29 *0.326°*	0.27 *0.473°*	– –	0.27 *0.52°*	**3.36%** **3.36%**
Emetine hydrochloride	0.12 *0.033°*	0.10 *0.062°*	0.10 *0.118°*	0.10 *0.171°*	0.10 *0.274°*	– –	
Ephedrine hydrochloride	0.32 *0.087°*	0.30 *0.169°*	0.29 *0.331°*	0.28 *0.489°*	– –	0.28 *0.52°*	**3.2%** **3.2%**
Ephedrine lactate	0.28 *0.075°*	0.26 *0.146°*	0.25 *0.285°*	0.24 *0.422°*	– –	0.24 *0.52°*	**3.72%** **3.72%**
Ephedrine sulfate	0.24 *0.070°*	0.23 *0.132°*	0.22 *0.247°*	0.20 *0.355°*	– –	0.20 *0.52°*	**4.54%** **4.54%**
Epinephrine bitartrate	0.18 *0.050°*	0.18 *0.098°*	0.17 *0.190°*	0.16 *0.281°*	0.16 *0.458°*	0.16 *0.52°*	**5.7%** **5.7%**
Epinephrine hydrochloride	0.30 *0.088°*	0.29 *0.165°*	0.27 *0.311°*	0.26 *0.451°*	– –	0.26 *0.52°*	**3.47%** **3.47%**
Ergonovine maleate	0.20 *0.055°*	0.16 *0.089°*	0.13 *0.143°*	– –	– –	– –	
Erythromycin glucoheptonate	0.08 *0.021°*	0.07 *0.042°*	0.07 *0.081°*	0.07 *0.120°*	0.07 *0.194°*	– –	
Erythromycin lactobionate	0.08 *0.020°*	0.07 *0.040°*	0.07 *0.078°*	0.07 *0.115°*	0.06 *0.187°*	– –	
Ethaverine hydrochloride	0.14 *0.037°*	0.12 *0.072°*	– –	– –	– –	– –	
Ethylenediamine	0.46 *0.130°*	0.44 *0.255°*	0.43 *0.501°*	– –	– –	– –	
Ethylhydrocupreine hydrochloride	0.22 *0.063°*	0.17 *0.098°*	0.13 *0.151°*	0.11 *0.196°*	0.09 *0.270°*	– –	
Ethylmorphine hydrochloride	0.16 *0.045°*	0.16 *0.088°*	0.15 *0.173°*	0.15 *0.257°*	0.15 *0.423°*	0.15 *0.52°*	**6.18%** **6.18%**

Chemical	Concentration of Solution, NaCl Equivalents						
	½%	1%	2%	3%	5%	At Isosmotic Concentration	
Ethylnorepinephrine hydrochloride	0.36 *0.104°*	0.32 *0.188°*	0.29 *0.334°*	0.28 *0.477°*	– –	0.27 *0.52°*	**3.32%** **3.32%**
Etidocaine hydrochloride	0.18 *0.051°*	0.18 *0.102°*	0.18 *0.204°*	0.18 *0.306°*	0.18 *0.510°*	0.18 *0.52°*	**5.08%** **5.08%**
Evans blue	0.06 *0.017°*	0.06 *0.033°*	0.06 *0.061°*	0.05 *0.091°*	0.05 *0.148°*	– –	
Ferric ammonium citrate, green	0.18 *0.054°*	0.17 *0.098°*	0.16 *0.179°*	0.15 *0.255°*	0.14 *0.397°*	– –	
Ferric cacodylate	0.10 *0.023°*	0.09 *0.046°*	0.08 *0.093°*	– –	– –	– –	
Ferrous gluconate	0.16 0.048°	0.15 *0.086°*	0.14 *0.154°*	0.12 *0.216°*	0.11 *0.330°*	– –	
Ferrous lactate	0.22 *0.062°*	0.21 *0.121°*	0.21 *0.237°*	– –	– –	– –	
Floxuridine	0.14 *0.040°*	0.13 *0.076°*	0.13 *0.147°*	0.12 *0.213°*	0.12 *0.335°*	0.12 *0.52°*	**8.47%** **8.47%**
Fluorescein sodium	0.36 *0.099°*	0.31 *0.182°*	0.29 *0.332°*	0.27 *0.472°*	– –	0.27 *0.52°*	**3.34%** **3.34%**
Fluphenazine dihydrochloride	0.14 *0.041°*	0.14 *0.082°*	0.12 *0.145°*	0.09 *0.155°*	– –	– –	
Folinic acid-SF calcium	0.06 *0.013°*	0.05 *0.026°*	0.05 *0.052°*	0.04 *0.077°*	0.04 *0.126°*	– –	
D-Fructose	0.18 *0.050°*	0.18 *0.100°*	0.18 *0.205°*	0.18 *0.310°*	0.18 *0.516°*	0.18 *0.52°*	**5.05%** **5.05%**
Furtrethonium iodide	0.24 *0.070°*	0.24 *0.133°*	0.22 *0.250°*	0.21 *0.360°*	– –	0.20 *0.52°*	**4.44%** **4.44%**
Galactose, anhydrous	0.18 *0.053°*	0.18 *0.105°*	0.18 *0.210°*	0.18 *0.316°*	– –	0.18 *0.52°*	**4.92%** **4.92%**
Gallamine triethiodide	0.08 *0.022°*	0.08 *0.046°*	0.08 *0.091°*	0.08 *0.136°*	0.08 *0.227°*	– –	
Gentamicin sulfate	0.05 *0.015°*	0.05 *0.030°*	0.05 *0.060°*	0.05 *0.093°*	0.05 *0.153°*	– –	
Glucoheptonate calcium	0.12 *0.037°*	0.12 *0.068°*	0.11 *0.124°*	0.10 *0.178°*	0.10 *0.275°*	– –	
Glucosulfone sodium	0.18 *0.049°*	0.16 *0.089°*	0.14 *0.162°*	0.13 *0.233°*	0.13 *0.366°*	– –	
D-Glucuronic acid	0.20 *0.061°*	0.20 *0.115°*	0.19 *0.220°*	0.19 *0.323°*	0.18 *0.517°*	0.18 *0.52°*	**5.02%** **5.02%**
L-Glutamic acid	0.25 *0.070°*	0.25 *0.144°*	0.25 *0.294°*	– –	– –	– –	
Glycerin	0.36 *0.104°*	0.35 *0.202°*	0.35 *0.403°*	– –	– –	0.35 *0.52°*	**2.6%** **2.6%**
Glycine	0.41 *0.118°*	0.41 *0.235°*	0.41 *0.470°*	– –	– –	0.41 *0.52°*	**2.19%** **2.19%**
Glycopyrrolate	0.15 *0.042°*	0.15 *0.084°*	0.15 *0.166°*	0.14 *0.242°*	0.13 *0.381°*	0.12 *0.52°*	**7.22%** **7.22%**

Isotonic Solutions (Continued)

Chemical	Concentration of Solution, NaCl Equivalents						
	½%	1%	2%	3%	5%	At Isosmotic Concentration	
Gnoscopine hydrochloride	0.11 *0.032°*	0.10 *0.056°*	0.09 *0.102°*	0.08 *0.144°*	0.08 *0.222°*	– –	
Gold sodium thiomalate	0.10 *0.032°*	0.10 *0.061°*	0.10 *0.111°*	0.09 *0.159°*	0.09 *0.250°*	– –	
Guanidine hydrochloride	0.72 *0.208°*	0.65 *0.376°*	– –	– –	– –	0.61 *0.52°*	**1.47%** **1.47%**
Heparin sodium	0.07 *0.021°*	0.07 *0.042°*	0.07 *0.084°*	0.07 *0.128°*	0.07 *0.213°*	0.07 *0.52°*	**12.2%** **12.2%**
Hetacillin potassium	0.17 *0.048°*	0.17 *0.095°*	0.17 *0.190°*	0.17 *0.284°*	0.17 *0.474°*	0.17 *0.52°*	**5.50%** **5.50%**
Hexafluorenium bromide	0.12 *0.033°*	0.11 *0.065°*	– –	– –	– –	– –	
Hexamethonium bromide	0.24 *0.069°*	0.22 *0.126°*	0.20 *0.233°*	0.19 *0.330°*	– –	0.18 *0.52°*	**4.99%** **4.99%**
Hexamethonium chloride	0.27 *0.078°*	0.27 *0.156°*	0.27 *0.315°*	0.27 *0.477°*	– –	0.27 *0.52°*	**3.3%** **3.3%**
Hexamethonium tartrate	0.16 *0.045°*	0.16 *0.089°*	0.16 *0.181°*	0.16 *0.271°*	0.16 *0.456°*	0.16 *0.52°*	**5.68%** **5.68%**
Hexamethylenamine sodium acetaminosalicylate	0.18 *0.049°*	0.18 *0.099°*	0.17 *0.199°*	0.17 *0.297°*	0.16 *0.485°*	0.16 *0.52°*	**5.48%** **5.48%**
Hexobarbital sodium	0.28 *0.078°*	0.26 *0.148°*	0.25 *0.282°*	0.24 *0.409°*	– –	0.23 *0.52°*	**3.88%** **3.88%**
Hexylcaine hydrochloride	0.28 *0.084°*	0.26 *0.151°*	0.24 *0.270°*	0.22 *0.380°*	– –	– –	
Histamine dihydrochloride	0.40 *0.115°*	0.40 *0.233°*	0.40 *0.466°*	– –	– –	0.40 *0.52°*	**2.24%** **2.24%**
Histamine phosphate	0.28 *0.080°*	0.25 *0.148°*	0.24 *0.274°*	0.23 *0.394°*	– –	0.22 *0.52°*	**4.1%** **4.1%**
Histidine monohydrochloride	0.30 *0.082°*	0.29 *0.162°*	0.28 *0.313°*	0.26 *0.460°*	– –	– –	
Homatropine hydrobromide	0.18 *0.049°*	0.17 *0.096°*	0.17 *0.189°*	0.16 *0.280°*	0.16 *0.461°*	0.16 *0.52°*	**5.67%** **5.67%**
Homatropine methyl bromide	0.20 *0.060°*	0.19 *0.106°*	0.17 *0.184°*	0.15 *0.256°*	0.13 *0.392°*	– –	
Hyaluronidase	0.01 *0.004°*	0.01 *0.007°*	0.01 *0.013°*	0.01 *0.020°*	0.01 *0.033°*	– –	
Hydralazine hydrochloride	0.44 *0.126°*	0.37 *0.213°*	– –	– –	– –	– –	
Hydrastine hydrochloride	0.18 *0.052°*	0.15 *0.089°*	0.14 *0.153°*	0.12 *0.208°*	0.11 *0.312°*	– –	
Hydromorphone hydrochloride	0.26 *0.073°*	0.22 *0.124°*	0.19 *0.211°*	0.17 *0.288°*	0.15 *0.429°*	0.14 *0.52°*	**6.39%** **6.39%**
Hydroxyamphetamine hydrobromide	0.28 *0.083°*	0.26 *0.156°*	0.26 *0.298°*	0.25 *0.435°*	– –	0.24 *0.52°*	**3.71%** **3.71%**
Hydroxychloroquine phosphate	0.20 *0.059°*	0.18 *0.104°*	0.16 *0.181°*	0.15 *0.256°*	0.13 *0.388°*	– –	

Isotonic Solutions (Continued)

Chemical	Concentration of Solution, NaCl Equivalents						
	½%	1%	2%	3%	5%	At Isosmotic Concentration	
8-Hydroxyquinoline sulfate	0.26 *0.071°*	0.21 *0.113°*	0.16 *0.180°*	0.14 *0.235°*	0.12 *0.330°*	0.11 *0.52°*	**9.75%** **9.75%**
Hydroxystilbamidine isethionate	0.20 *0.060°*	0.16 *0.090°*	0.12 *0.137°*	0.10 *0.170°*	0.07 *0.216°*	– –	
Hydroxyzine hydrochloride	0.26 *0.075°*	0.25 *0.138°*	0.22 *0.251°*	0.20 *0.345°*	0.16 *0.458°*	0.14 *0.52°*	**6.32%** **6.32%**
Hyoscyamine hydrobromide	0.20 *0.059°*	0.19 *0.106°*	0.17 *0.191°*	0.16 *0.270°*	0.14 *0.417°*	– –	
Hyoscyamine sulfate	0.17 *0.048°*	0.15 *0.085°*	0.13 *0.149°*	0.12 *0.208°*	0.11 *0.312°*	– –	
Imipramine hydrochloride	0.20 *0.058°*	0.20 *0.110°*	– –	– –	– –	– –	
Indigotindisulfonate sodium	0.30 *0.085°*	0.30 *0.172°*	– –	– –	– –	– –	
o-Iodohippurate sodium	0.16 0.047°	0.16 *0.091°*	0.16 *0.180°*	0.15 *0.267°*	0.15 *0.442°*	0.15 *0.52°*	**5.92%** **5.92%**
Iodophthalein sodium	0.20 *0.055°*	0.17 *0.093°*	0.14 *0.159°*	0.12 *0.216°*	0.11 *0.319°*	0.09 *0.52°*	**9.58%** **9.58%**
Iodopyracet	0.12 *0.036°*	0.11 *0.067°*	0.11 *0.127°*	0.11 *0.185°*	0.10 *0.298°*	0.10 *0.52°*	**9.21%** **9.21%**
Iodopyracet diethylamine	0.14 *0.035°*	0.12 0.068°	0.12 *0.130°*	0.11 *0.190°*	0.11 *0.308°*	0.10 *0.52°*	**8.73%** **8.73%**
Isoetharine hydrochloride	0.24 *0.068°*	0.23 *0.132°*	0.22 *0.250°*	0.21 *0.368°*	– –	0.21 *0.52°*	**4.27%** **4.27%**
Isometheptene mucate	0.18 *0.048°*	0.18 *0.095°*	0.18 *0.196°*	0.18 *0.302°*	– –	0.18 *0.52°*	**4.95%** **4.95%**
Isoniazid	0.28 *0.079°*	0.25 *0.144°*	0.23 *0.266°*	0.22 *0.378°*	– –	0.21 *0.52°*	**4.35%** **4.35%**
Isoproterenol sulfate	0.14 *0.039°*	0.14 *0.078°*	0.14 *0.156°*	0.14 *0.234°*	0.14 *0.389°*	0.14 *0.52°*	**6.65%** **6.65%**
Kanamycin sulfate	0.08 *0.021°*	0.07 *0.041°*	0.07 *0.083°*	0.07 *0.125°*	0.07 *0.210°*	– –	
Ketamine hydrochloride	0.21 *0.061°*	0.21 *0.122°*	0.21 *0.244°*	0.21 *0.366°*	– –	0.21 *0.52°*	**4.29%** **4.29%**
Lactic acid	0.44 *0.124°*	0.41 *0.237°*	0.39 *0.457°*	– –	– –	0.39 *0.52°*	**2.3%** **2.3%**
Lactose	0.06 *0.019°*	0.07 *0.040°*	0.08 *0.088°*	0.08 *0.139°*	0.09 *0.246°*	0.09 *0.52°*	**9.75%** **9.75%**
Levallorphan tartrate	0.13 *0.036°*	0.13 *0.073°*	0.13 *0.143°*	0.12 *0.210°*	0.12 *0.329°*	0.10 *0.52°*	**9.40%** **9.40%**
Levorphanol tartrate	0.12 *0.033°*	0.12 *0.067°*	0.12 *0.136°*	0.12 *0.203°*	– –	– –	
Lidocaine hydrochloride	0.22 *0.065°*	0.22 *0.125°*	0.21 *0.243°*	0.21 *0.358°*	– –	0.20 *0.52°*	**4.42%** **4.42%**
Lincomycin hydrochloride	0.16 *0.045°*	0.16 *0.090°*	0.15 *0.170°*	0.14 *0.247°*	0.14 *0.400°*	0.14 *0.52°*	**6.60%** **6.60%**

Isotonic Solutions (Continued)

Chemical	Concentration of Solution, NaCl Equivalents						
	½%	1%	2%	3%	5%	At Isosmotic Concentration	
Lobeline hydrochloride	0.16 *0.047°*	0.16 *0.091°*	0.16 *0.174°*	– –	– –	– –	
Lyapolate sodium	0.10 *0.025°*	0.09 *0.051°*	0.09 *0.103°*	0.09 *0.157°*	0.09 *0.263°*	0.09 *0.52°*	**9.96%** **9.96%**
Mafenide hydrochloride	0.27 *0.075°*	0.27 *0.153°*	0.27 *0.303°*	0.26 *0.448°*	– –	0.25 *0.52°*	**3.55%** **3.55%**
Magnesium chloride	0.48 *0.136°*	0.45 *0.260°*	0.45 *0.515°*	– –	– –	0.45 *0.52°*	**2.02%** **2.02%**
Magnesium sulfate	0.18 *0.049°*	0.17 *0.094°*	0.16 *0.178°*	0.15 *0.261°*	0.15 *0.419°*	0.14 *0.52°*	**6.3%** **6.3%**
Magnesium sulfate, anhydrous	0.34 *0.093°*	0.32 *0.184°*	0.30 *0.345°*	0.29 *0.495°*	– –	0.28 *0.52°*	**3.18%** **3.18%**
Mannitol	0.16 *0.047°*	0.17 *0.099°*	0.17 *0.200°*	0.17 *0.304°*	0.18 *0.514°*	0.18 *0.52°*	**5.07%** **5.07%**
Menadiol sodium diphosphate	0.27 *0.078°*	0.25 *0.142°*	0.23 *0.262°*	0.21 *0.372°*	– –	– –	
Menadione sodium bisulfite	0.20 *0.057°*	0.20 *0.110°*	0.19 *0.213°*	0.18 *0.315°*	0.18 *0.511°*	0.18 *0.52°*	**5.07%** **5.07%**
Meperidine hydrochloride	0.24 *0.066°*	0.22 *0.124°*	0.21 *0.235°*	0.20 *0.340°*	– –	0.19 *0.52°*	**4.8%** **4.8%**
Mephenesin	0.19 *0.055°*	0.19 *0.108°*	– –	– –	– –	– –	
Mephentermine sulfate	0.24 *0.069°*	0.22 *0.131°*	0.21 *0.245°*	0.20 *0.346°*	– –	0.19 *0.52°*	**4.74%** **4.74%**
Mepivacaine hydrochloride	0.21 *0.060°*	0.21 *0.116°*	0.20 *0.230°*	0.20 *0.342°*	– –	0.20 *0.52°*	**4.6%** **4.6%**
Merbromin	0.16 *0.044°*	0.14 *0.081°*	0.12 *0.136°*	0.11 *0.185°*	0.09 *0.272°*	– –	
Mercaptomerin sodium	0.19 *0.056°*	0.18 *0.107°*	0.18 *0.206°*	0.18 *0.308°*	0.17 *0.494°*	– –	
Mercuric cyanide	0.16 *0.047°*	0.15 *0.087°*	0.15 *0.166°*	0.14 *0.239°*	0.13 *0.383°*	– –	
Mercurophylline	0.14 *0.042°*	0.13 *0.073°*	0.11 *0.126°*	0.10 *0.175°*	0.09 *0.262°*	– –	
Mercury bichloride	0.14 *0.038°*	0.13 *0.073°*	0.12 *0.140°*	0.12 *0.206°*	0.10 *0.334°*	– –	
Mersalyl	0.14 *0.041°*	0.12 *0.063°*	0.11 *0.122°*	0.11 *0.181°*	0.10 *0.294°*	0.10 *0.52°*	**9.06%** **9.06%**
Mesoridazine besylate	0.10 *0.024°*	0.07 *0.040°*	0.05 *0.058°*	0.04 *0.071°*	0.03 *0.087°*	– –	
Metaraminol bitartrate	0.20 *0.060°*	0.20 *0.112°*	0.19 *0.210°*	0.18 *0.308°*	0.17 *0.505°*	0.17 *0.52°*	**5.17%** **5.17%**
Methacholine bromide	0.29 *0.087°*	0.28 *0.164°*	0.26 *0.298°*	0.24 *0.425°*	– –	0.24 *0.52°*	**3.77%** **3.77%**
Methacholine chloride	0.34 *0.099°*	0.32 *0.181°*	0.30 *0.388°*	0.28 *0.494°*	– –	0.28 *0.52°*	**3.21%** **3.21%**

Isotonic Solutions (Continued)

Chemical	Concentration of Solution, NaCl Equivalents						
	½%	1%	2%	3%	5%	At Isosmotic Concentration	
Methadone hydrochloride	0.22 *0.060°*	0.18 *0.101°*	0.15 *0.171°*	0.14 *0.232°*	0.12 *0.344°*	0.10 *0.52°*	**8.59%** **8.59%**
Methamphetamine hydrochloride	0.38 *0.112°*	0.37 *0.208°*	0.34 *0.388°*	— —	— —	0.33 *0.52°*	**2.75%** **2.75%**
Methantheline bromide	0.22 *0.063°*	0.15 *0.089°*	0.11 *0.124°*	0.09 *0.151°*	0.07 *0.190°*	— —	
Methapyrilene hydrochloride	0.20 *0.060°*	0.19 *0.112°*	0.18 *0.213°*	0.18 *0.308°*	0.17 *0.488°*	0.17 *0.52°*	**5.35%** **5.35%**
Methdilazine hydrochloride	0.12 *0.035°*	0.10 *0.056°*	0.08 *0.080°*	0.06 *0.093°*	0.04 *0.112°*	— —	
Methenamine	0.22 *0.061°*	0.23 *0.129°*	0.24 *0.271°*	0.24 *0.418°*	— —	0.24 *0.52°*	**3.68%** **3.68%**
Methicillin sodium	0.18 *0.050°*	0.18 *0.099°*	0.17 *0.192°*	0.16 *0.281°*	0.15 *0.445°*	0.15 *0.52°*	**6.00%** **6.00%**
Methiodal sodium	0.24 *0.068°*	0.24 *0.136°*	0.24 *0.274°*	0.24 *0.410°*	— —	0.24 *0.52°*	**3.81%** **3.81%**
Methionine	0.32 *0.091°*	0.28 *0.160°*	0.25 *0.285°*	— —	— —	— —	
Methitural sodium	0.26 *0.074°*	0.25 *0.142°*	0.24 *0.275°*	0.23 *0.407°*	— —	0.23 *0.52°*	**3.85%** **3.85%**
Methocarbamol	0.10 *0.030°*	0.10 *0.060°*	— —	— —	— —	— —	
Methotrimeprazine hydrochloride	0.12 *0.034°*	0.10 *0.060°*	0.07 *0.077°*	0.06 *0.094°*	0.04 *0.125°*	— —	
Methoxamine hydrochloride	0.28 *0.078°*	0.26 *0.148°*	0.25 *0.281°*	0.24 *0.416°*	— —	0.24 *0.52°*	**3.82%** **3.82%**
Methoxyphenamine hydrochloride	0.26 *0.075°*	0.26 *0.150°*	0.26 *0.300°*	0.26 *0.450°*	— —	0.26 *0.52°*	**3.47%** **3.47%**
Methylatropine bromide	0.15 *0.045°*	0.15 *0.086°*	0.14 *0.162°*	0.14 *0.236°*	0.13 *0.380°*	0.13 *0.52°*	**7.03%** **7.03%**
Methyldopa ethyl ester hydrochloride	0.21 *0.063°*	0.21 *0.122°*	0.21 *0.244°*	0.21 *0.365°*	— —	0.21 *0.52°*	**4.28%** **4.28%**
Methylergonovine maleate	0.10 *0.028°*	0.10 *0.056°*	— —	— —	— —	— —	
N-Methylglucamine	0.20 *0.057°*	0.20 *0.111°*	0.18 *0.214°*	0.18 *0.315°*	0.18 *0.517°*	0.18 *0.52°*	**5.02%** **5.02%**
Methylphenidate hydrochloride	0.22 *0.065°*	0.22 *0.127°*	0.22 *0.258°*	0.22 *0.388°*	— —	0.22 *0.52°*	**4.07%** **4.07%**
Methylprednisolone sodium succinate	0.10 *0.025°*	0.09 *0.051°*	0.09 *0.102°*	0.08 *0.143°*	0.07 *0.200°*	— —	
Metoclopramide hydrochloride	0.16 *0.045°*	0.15 *0.084°*	0.13 *0.155°*	0.12 *0.216°*	0.11 *0.315°*	— —	
Metrizamide	0.04 *0.010°*	0.04 *0.020°*	0.03 *0.040°*	0.03 *0.060°*	— —	— —	
Minocycline hydrochloride	0.10 *0.030°*	0.10 *0.058°*	0.09 *0.107°*	0.08 *0.146°*	— —	— —	

Isotonic Solutions (Continued)

Chemical	Concentration of Solution, NaCl Equivalents						
	½%	1%	2%	3%	5%	At Isosmotic Concentration	
Monoethanolamine	0.53 *0.154°*	0.53 *0.306°*	– –	– –	– –	0.53 *0.52°*	**1.70%** **1.70%**
Morphine hydrochloride	0.16 *0.044°*	0.15 *0.086°*	0.15 *0.168°*	0.14 *0.248°*	– –	– –	
Morphine nitrate	0.22 *0.061°*	0.19 *0.106°*	0.16 *0.184°*	0.15 *0.255°*	– –	– –	
Morphine sulfate	0.16 *0.046°*	0.14 *0.078°*	0.12 *0.131°*	0.11 *0.178°*	0.09 *0.258°*	– –	
Naepaine hydrochloride	0.24 *0.067°*	0.22 *0.126°*	0.20 *0.233°*	0.19 *0.338°*	– –	0.18 *0.52°*	**4.98%** **4.98%**
Nafcillin sodium	0.14 *0.039°*	0.14 *0.078°*	0.14 *0.158°*	0.13 *0.219°*	0.10 *0.285°*	– –	
Nalbuphine hydrochloride	0.16 *0.045°*	0.15 *0.085°*	0.14 *0.158°*	– –	– –	– –	
Nalorphine hydrochloride	0.24 *0.070°*	0.21 *0.121°*	0.18 *0.210°*	0.17 *0.288°*	0.15 *0.434°*	0.14 *0.52°*	**6.36%** **6.36%**
Naloxone hydrochloride	0.14 *0.042°*	0.14 *0.083°*	0.14 *0.158°*	0.13 *0.230°*	0.13 *0.367°*	0.11 *0.52°*	**8.07%** **8.07%**
Naphazoline hydrochloride	0.30 *0.084°*	0.27 *0.155°*	0.25 *0.286°*	0.24 *0.413°*	– –	0.22 *0.52°*	**3.99%** **3.99%**
Neoarsphenamine	0.42 *0.116°*	0.40 *0.228°*	0.39 *0.449°*	– –	– –	0.39 *0.52°*	**2.32%** **2.32%**
Neomycin sulfate	0.14 *0.041°*	0.12 *0.067°*	0.10 *0.112°*	0.09 *0.154°*	0.08 *0.223°*	– –	
Neostigmine bromide	0.23 *0.065°*	0.22 *0.123°*	0.20 *0.230°*	0.19 *0.333°*	– –	– –	
Neostigmine methyl sulfate	0.22 *0.056°*	0.20 *0.108°*	0.18 *0.208°*	0.18 *0.306°*	0.17 *0.500°*	0.17 *0.52°*	**5.22%** **5.22%**
Nicotinamide	0.30 *0.083°*	0.26 *0.148°*	0.23 *0.264°*	0.21 *0.371°*	– –	0.20 *0.52°*	**4.49%** **4.49%**
Nicotinic acid	0.26 *0.074°*	0.25 *0.145°*	– –	– –	– –	– –	
Nikethamide	0.20 *0.053°*	0.18 *0.100°*	0.17 *0.190°*	0.16 *0.276°*	0.15 *0.443°*	0.15 *0.52°*	**5.94%** **5.94%**
Novobiocin sodium	0.10 *0.025°*	0.08 *0.046°*	0.08 *0.086°*	0.07 *0.122°*	0.07 *0.190°*	– –	
Oleandomycin phosphate	0.08 *0.017°*	0.08 *0.038°*	0.08 *0.084°*	0.08 *0.129°*	0.08 *0.255°*	0.08 *0.52°*	**10.82%** **10.82%**
Orphenadrine citrate	0.13 *0.037°*	0.13 *0.074°*	0.13 *0.144°*	0.12 *0.204°*	0.10 *0.285°*	– –	
Oxacillin sodium	0.18 *0.050°*	0.17 *0.095°*	0.16 *0.177°*	0.15 *0.257°*	0.14 *0.408°*	0.14 *0.52°*	**6.64%** **6.64%**
Oxophenarsine hydrochloride	0.24 *0.067°*	0.24 *0.138°*	0.24 *0.281°*	0.24 *0.425°*	– –	0.24 *0.52°*	**3.67%** **3.67%**
Oxycodone	0.16 *0.043°*	0.14 *0.081°*	0.14 *0.155°*	0.13 *0.226°*	0.13 *0.363°*	0.12 *0.52°*	**7.4%** **7.4%**

Isotonic Solutions (Continued)

Chemical	Concentration of Solution, NaCl Equivalents						
	½%	1%	2%	3%	5%	At Isosmotic Concentration	
Oxymetazoline hydrochloride	0.22 *0.063°*	0.22 *0.124°*	0.20 *0.232°*	0.19 *0.335°*	– –	0.18 *0.52°*	**4.92%** **4.92%**
Oxymorphone hydrochloride	0.16 *0.044°*	0.16 *0.088°*	0.15 *0.168°*	0.14 *0.244°*	0.13 *0.382°*	– –	
Oxytetracycline hydrochloride	0.17 *0.052°*	0.14 *0.081°*	0.11 *0.113°*	0.08 *0.141°*	– –	– –	
Papaverine hydrochloride	0.10 *0.028°*	0.10 *0.060°*	0.10 *0.121°*	– –	– –	– –	
Paraldehyde	0.25 *0.071°*	0.25 *0.142°*	0.25 *0.288°*	0.25 *0.430°*	– –	0.25 *0.52°*	**3.65%** **3.65%**
Parethoxycaine hydrochloride	0.20 *0.058°*	0.20 *0.110°*	– –	– –	– –	– –	
Pargyline hydrochloride	0.30 *0.093°*	0.29 *0.165°*	0.29 *0.327°*	0.28 *0.491°*	– –	0.28 *0.52°*	**3.18%** **3.18%**
Pentazocine lactate	0.15 *0.042°*	0.15 *0.085°*	0.15 *0.169°*	0.15 *0.253°*	0.15 *0.420°*	– –	
Pentobarbital sodium	0.26 *0.076°*	0.25 *0.143°*	0.24 *0.270°*	0.23 *0.393°*	– –	– –	
Pentolinium tartrate	0.18 *0.050°*	0.17 *0.097°*	0.16 *0.186°*	0.15 *0.268°*	0.15 *0.440°*	– –	
Pentylenetetrazole	0.24 *0.069°*	0.22 *0.127°*	0.21 *0.236°*	0.19 *0.337°*	– –	0.18 *0.52°*	**4.91%** **4.91%**
Phenacaine hydrochloride	0.22 *0.061°*	0.20 *0.108°*	– –	– –	– –	– –	
Phenarsone sulfoxylate	0.36 *0.104°*	0.33 *0.193°*	0.31 *0.353°*	0.29 *0.505°*	– –	0.29 *0.52°*	**3.07%** **3.07%**
Phenindamine tartrate	0.22 *0.064°*	0.17 *0.100°*	0.14 *0.158°*	0.12 *0.204°*	0.10 *0.285°*	– –	
Pheniramine maleate	0.18 *0.052°*	0.16 *0.095°*	0.15 *0.173°*	0.14 *0.247°*	0.13 *0.383°*	– –	
Phenobarbital sodium	0.24 *0.069°*	0.24 *0.135°*	0.23 *0.267°*	0.23 *0.396°*	– –	0.23 *0.52°*	**3.95%** **3.95%**
Phenol	0.38 *0.104°*	0.35 *0.199°*	0.33 *0.381°*	– –	– –	0.32 *0.52°*	**2.8%** **2.8%**
Phentolamine mesylate	0.18 *0.052°*	0.17 *0.096°*	0.16 *0.173°*	0.14 *0.244°*	0.13 *0.364°*	0.11 *0.52°*	**8.23%** **8.23%**
Phenylbutazone sodium	0.19 *0.054°*	0.18 *0.104°*	0.17 *0.202°*	0.17 *0.298°*	0.17 *0.488°*	0.17 *0.52°*	**5.34%** **5.34%**
Phenylephrine hydrochloride	0.34 *0.096°*	0.32 *0.184°*	0.31 *0.354°*	0.30 *0.520°*	– –	0.30 *0.52°*	**3.0%** **3.0%**
Phenylephrine tartrate	0.20 *0.055°*	0.19 *0.104°*	0.17 *0.195°*	0.16 *0.282°*	0.16 *0.448°*	0.15 *0.52°*	**5.9%** **5.9%**
Phenylethyl alcohol	0.25 *0.070°*	0.25 *0.141°*	0.25 *0.283°*	– –	– –	– –	
Phenylpropanolamine hydrochloride	0.40 *0.117°*	0.38 *0.218°*	0.35 *0.406°*	– –	– –	0.35 *0.52°*	**2.6%** **2.6%**

Isotonic Solutions (Continued)

Chemical	Concentration of Solution, NaCl Equivalents						
	½%	1%	2%	3%	5%	At Isosmotic Concentration	
Phenylpropylmethylamine hydrochloride	0.42 *0.123°*	0.38 *0.220°*	0.34 *0.397°*	— —	— —	0.33 *0.52°*	**2.7%** **2.7%**
Physostigmine salicylate	0.16 *0.045°*	0.16 *0.090°*	— —	— —	— —	— —	
Physostigmine sulfate	0.14 *0.040°*	0.13 *0.076°*	0.13 *0.146°*	0.12 *0.214°*	0.12 *0.344°*	0.12 *0.52°*	**7.74%** **7.74%**
Pilocarpine hydrochloride	0.24 *0.069°*	0.24 *0.134°*	0.23 *0.262°*	0.22 *0.387°*	— —	0.22 *0.52°*	**4.08%** **4.08%**
Pilocarpine nitrate	0.24 *0.070°*	0.23 *0.131°*	0.21 *0.247°*	0.20 *0.355°*	— —	— —	
Piperacillin sodium	0.11 *0.032°*	0.11 *0.063°*	0.11 *0.123°*	0.10 *0.175°*	— —	— —	
Piperocaine hydrochloride	0.22 *0.066°*	0.21 *0.120°*	0.19 *0.220°*	0.19 *0.319°*	0.17 *0.499°*	— —	
Piridocaine hydrochloride	0.24 *0.072°*	0.24 *0.139°*	— —	— —	— —	— —	
Polyethylene glycol 300	0.12 *0.034°*	0.12 *0.069°*	0.12 *0.141°*	0.12 *0.216°*	0.13 *0.378°*	0.13 *0.52°*	**6.73%** **6.73%**
Polyethylene glycol 400	0.08 *0.022°*	0.08 *0.047°*	0.09 *0.098°*	0.09 *0.153°*	0.09 *0.272°*	0.11 *0.52°*	**8.50%** **8.50%**
Polyethylene glycol 1500	0.06 *0.015°*	0.06 *0.036°*	0.07 *0.078°*	0.07 *0.120°*	0.07 *0.215°*	0.09 *0.52°*	**10.00%** **10.00%**
Polyethylene glycol 1540	0.02 *0.005°*	0.02 *0.012°*	0.02 *0.028°*	0.03 *0.047°*	0.03 *0.094°*	— —	
Polyethylene glycol 4000	0.02 *0.004°*	0.02 *0.008°*	0.02 *0.020°*	0.02 *0.033°*	0.02 *0.067°*	— —	
Polymyxin B sulfate	0.10 *0.033°*	0.09 *0.049°*	0.07 *0.075°*	0.06 *0.098°*	0.04 *0.131°*	— —	
Polysorbate 80	0.02 *0.005°*	0.02 *0.010°*	0.02 *0.020°*	0.02 *0.032°*	0.02 *0.055°*	— —	
Polyvinyl alcohol (99% hydrolyzed)	0.02 *0.004°*	0.02 *0.008°*	0.02 *0.020°*	0.02 *0.035°*	0.03 *0.075°*	— —	
Potassium acetate	0.59 *0.172°*	0.59 *0.342°*	— —	— —	— —	0.59 *0.52°*	**1.53%** **1.53%**
Potassium chlorate	0.50 *0.140°*	0.49 *0.278°*	— —	— —	— —	0.48 *0.52°*	**1.88%** **1.88%**
Potassium chloride	0.76 *0.219°*	0.76 *0.439°*	— —	— —	— —	0.76 *0.52°*	**1.19%** **1.19%**
Potassium iodide	0.34 *0.104°*	0.34 *0.205°*	0.34 *0.402°*	— —	— —	0.34 *0.52°*	**2.59%** **2.59%**
Potassium nitrate	0.58 *0.163°*	0.56 *0.323°*	— —	— —	— —	0.56 *0.52°*	**1.62%** **1.62%**
Potassium permanganate	0.39 *0.112°*	0.39 *0.224°*	0.39 *0.449°*	— —	— —	— —	
Potassium phosphate	0.48 *0.139°*	0.46 *0.265°*	0.44 *0.501°*	— —	— —	0.43 *0.52°*	**2.08%** **2.08%**

Isotonic Solutions (Continued)

Chemical	Concentration of Solution, NaCl Equivalents						
	½%	1%	2%	3%	5%	At Isosmotic Concentration	
Potassium phosphate, monobasic	0.48 *0.133°*	0.44 *0.252°*	0.42 *0.480°*	– –	– –	0.41 *0.52°*	**2.18%** **2.18%**
Potassium sulfate	0.46 *0.132°*	0.44 *0.254°*	0.43 *0.495°*	– –	– –	0.43 *0.52°*	**2.11%** **2.11%**
Potassium thiocyanate	0.61 *0.180°*	0.59 *0.341°*	– –	– –	– –	0.59 *0.52°*	**1.52%** **1.52%**
Povidone	0.01 *0.004°*	0.01 *0.008°*	0.01 *0.010°*	0.01 *0.017°*	0.01 *0.035°*	– –	
Pralidoxime chloride	0.32 *0.092°*	0.32 *0.183°*	0.32 *0.364°*	– –	– –	0.32 *0.52°*	**2.87%** **2.87%**
Pramoxine hydrochloride	0.18 *0.056°*	0.18 *0.104°*	0.17 *0.196°*	0.15 *0.253°*	0.10 *0.281°*	– –	
Prilocaine hydrochloride	0.22 *0.062°*	0.22 *0.125°*	0.22 *0.250°*	0.22 *0.375°*	– –	0.22 *0.52°*	**4.18%** **4.18%**
Probarbital calcium	0.28 *0.079°*	0.25 *0.144°*	– –	– –	– –	– –	
Probarbital sodium	0.38 *0.110°*	0.32 *0.186°*	0.30 *0.353°*	0.29 *0.505°*	– –	0.29 *0.52°*	**3.1%** **3.1%**
Procainamide hydrochloride	0.24 *0.071°*	0.22 *0.128°*	0.20 *0.231°*	0.19 *0.330°*	0.17 *0.505°*	– –	
Procaine hydrochloride	0.24 *0.065°*	0.21 *0.122°*	0.20 *0.227°*	0.19 *0.327°*	0.18 *0.515°*	0.18 *0.52°*	**5.05%** **5.05%**
Prochlorperazine edisylate	0.08 *0.020°*	0.06 *0.033°*	0.05 *0.048°*	0.03 *0.056°*	0.02 *0.065°*	– –	
Promazine hydrochloride	0.18 *0.050°*	0.13 *0.077°*	0.09 *0.102°*	0.07 *0.112°*	0.05 *0.137°*	– –	
Promethazine hydrochloride	0.28 *0.084°*	0.18 *0.112°*	0.12 *0.151°*	0.10 *0.180°*	0.07 *0.224°*	– –	
Propantheline bromide	0.11 *0.032°*	0.11 *0.064°*	– –	– –	– –	– –	
Proparacaine hydrochloride	0.16 *0.044°*	0.15 *0.086°*	0.15 *0.169°*	0.14 *0.247°*	0.13 *0.380°*	0.12 *0.52°*	**7.46%** **7.46%**
Propiomazine hydrochloride	0.18 *0.050°*	0.15 *0.084°*	0.12 *0.133°*	0.10 *0.165°*	0.08 *0.215°*	– –	
Propoxycaine hydrochloride	0.22 *0.063°*	0.19 *0.112°*	0.17 *0.199°*	0.16 *0.281°*	0.15 *0.425°*	– –	
Propranolol hydrochloride	0.20 *0.060°*	0.20 *0.122°*	0.20 *0.230°*	– –	– –	– –	
Propylene glycol	0.45 *0.131°*	0.45 *0.262°*	0.45 *0.520°*	– –	– –	0.45 *0.52°*	**2.0%** **2.0%**
Pyrathiazine hydrochloride	0.22 *0.065°*	0.17 *0.095°*	0.11 *0.123°*	0.08 *0.140°*	0.06 *0.170°*	– –	
Pyridostigmine bromide	0.22 *0.062°*	0.22 *0.125°*	0.22 *0.250°*	0.22 *0.377°*	– –	0.22 *0.52°*	**4.13%** **4.13%**
Pyridoxine hydrochloride	0.41 *0.118°*	0.36 *0.208°*	0.32 *0.367°*	0.29 *0.512°*	– –	– –	

Isotonic Solutions (Continued)

Chemical	Concentration of Solution, NaCl Equivalents						
	½%	1%	2%	3%	5%	At Isosmotic Concentration	
Pyrilamine maleate	0.24 *0.072°*	0.18 *0.106°*	0.14 *0.156°*	0.11 *0.195°*	0.09 *0.258°*	– –	
Quinacrine hydrochloride	0.20 *0.056°*	0.18 *0.100°*	0.16 *0.178°*	– –	– –	– –	
Quinacrine mesylate	0.12 *0.034°*	0.11 *0.064°*	0.11 *0.122°*	0.10 *0.178°*	0.10 *0.285°*	– –	
Quinidine gluconate	0.14 *0.037°*	0.12 *0.069°*	0.11 *0.124°*	0.10 *0.178°*	– –	– –	
Quinidine sulfate	0.14 *0.041°*	0.10 *0.060°*	0.08 *0.087°*	– –	– –	– –	
Quinine bisulfate	0.09 *0.029°*	0.09 *0.056°*	0.09 *0.107°*	0.09 *0.156°*	– –	– –	
Quinine dihydrochloride	0.26 *0.072°*	0.23 *0.129°*	0.20 *0.232°*	0.19 *0.330°*	0.18 *0.513°*	0.18 *0.52°*	**5.07%** **5.07%**
Quinine hydrochloride	0.16 *0.043°*	0.14 *0.077°*	0.13 *0.140°*	0.11 *0.197°*	– –	– –	
Quinine urea hydrochloride	0.26 *0.073°*	0.23 *0.135°*	0.22 *0.253°*	0.21 *0.370°*	– –	0.20 *0.52°*	**4.5%** **4.5%**
Racephedrine hydrochloride	0.32 *0.093°*	0.31 *0.178°*	0.30 *0.346°*	0.30 *0.512°*	– –	0.29 *0.52°*	**3.07%** **3.07%**
Resorcinol	0.28 *0.082°*	0.28 *0.161°*	0.28 *0.319°*	0.27 *0.473°*	– –	0.27 *0.52°*	**3.3%** **3.3%**
Riboflavin phosphate (sodium)	0.08 *0.022°*	0.08 *0.047°*	0.08 *0.098°*	0.08 *0.150°*	– –	– –	
Rolitetracycline	0.11 *0.032°*	0.11 *0.064°*	0.10 *0.113°*	0.09 *0.158°*	0.07 *0.204°*	– –	
Rose bengal	0.08 *0.020°*	0.07 *0.040°*	0.07 *0.083°*	0.07 *0.124°*	0.07 *0.198°*	0.06 *0.52°*	**14.9%** **14.9%**
Rose bengal B	0.08 *0.022°*	0.08 *0.044°*	0.08 *0.087°*	0.08 *0.150°*	0.08 *0.218°*	– –	
Scopolamine hydrobromide	0.12 *0.034°*	0.12 *0.068°*	0.12 *0.135°*	0.12 *0.201°*	0.12 *0.333°*	0.11 *0.52°*	**7.85%** **7.85%**
Scopolamine methyl nitrate	0.18 *0.049°*	0.16 *0.091°*	0.15 *0.171°*	0.14 *0.244°*	0.13 *0.387°*	0.13 *0.52°*	**6.95%** **6.95%**
Secobarbital sodium	0.25 *0.071°*	0.24 *0.139°*	0.23 *0.272°*	0.23 *0.404°*	– –	0.23 *0.52°*	**3.9%** **3.9%**
Silver nitrate	0.33 *0.095°*	0.33 *0.190°*	0.33 *0.380°*	– –	– –	0.33 *0.52°*	**2.74%** **2.74%**
Silver protein, mild	0.17 *0.047°*	0.17 *0.095°*	0.17 *0.189°*	0.17 *0.283°*	0.16 *0.472°*	0.16 *0.52°*	**5.51%** **5.51%**
Silver protein, strong	0.12 *0.033°*	0.08 *0.047°*	0.06 *0.066°*	0.05 *0.081°*	0.04 *0.107°*	– –	
Sodium acetate	0.47 *0.136°*	0.46 *0.267°*	0.45 *0.513°*	– –	– –	0.45 *0.52°*	**2.03%** **2.03%**
Sodium acetate, anhydrous	0.80 *0.226°*	0.77 *0.443°*	– –	– –	– –	0.76 *0.52°*	**1.18%** **1.18%**

Isotonic Solutions (Continued)

Chemical	Concentration of Solution, NaCl Equivalents						
	½%	1%	2%	3%	5%	At Isosmotic Concentration	
Sodium antimonyl tartrate	0.14 *0.039°*	0.13 *0.074°*	0.13 *0.142°*	0.12 *0.208°*	0.12 *0.338°*	0.11 *0.52°*	7.9% 7.9%
Sodium arsenate, dibasic	0.26 *0.074°*	0.25 *0.143°*	0.25 *0.278°*	0.24 *0.410°*	– –	0.24 *0.52°*	3.83% 3.83%
Sodium ascorbate	0.34 *0.097°*	0.32 *0.186°*	0.30 *0.350°*	– –	– –	0.30 *0.52°*	2.99% 2.99%
Sodium benzoate	0.40 *0.116°*	0.40 *0.232°*	0.40 *0.464°*	– –	– –	0.40 *0.52°*	2.25% 2.25%
Sodium bicarbonate	0.68 *0.197°*	0.65 *0.381°*	– –	– –	– –	0.65 *0.52°*	1.39% 1.39%
Sodium biphosphate ($1H_2O$)	0.44 *0.123°*	0.40 *0.228°*	0.38 *0.434°*	– –	– –	0.37 *0.52°*	2.45% 2.45%
Sodium biphosphate ($2H_2O$)	0.40 *0.109°*	0.36 *0.202°*	0.34 *0.384°*	– –	– –	0.32 *0.52°*	2.77% 2.77%
Sodium biphosphate, anhydrous	0.50 *0.142°*	0.46 *0.263°*	0.43 *0.499°*	– –	– –	0.43 *0.52°*	2.1% 2.1%
Sodium bismuth thioglycolate	0.20 *0.055°*	0.19 *0.107°*	0.18 *0.208°*	0.18 *0.303°*	0.17 *0.493°*	0.17 *0.52°*	5.29% 5.29%
Sodium bisulfite	0.64 *0.186°*	0.61 *0.353°*	– –	– –	– –	0.60 *0.52°*	1.5% 1.5%
Sodium borate	0.48 *0.137°*	0.42 *0.241°*	0.37 *0.421°*	– –	– –	0.35 *0.52°*	2.6% 2.6%
Sodium bromide	0.58 *0.166°*	0.58 *0.329°*	– –	– –	– –	0.57 *0.52°*	1.6% 1.6%
Sodium cacodylate	0.38 *0.104°*	0.32 *0.188°*	0.30 *0.339°*	0.28 *0.480°*	– –	0.27 *0.52°*	3.3% 3.3%
Sodium carbonate, anhydrous	0.74 *0.214°*	0.70 *0.404°*	– –	– –	– –	0.68 *0.52°*	1.32% 1.32%
Sodium carbonate, monohydrated	0.64 *0.183°*	0.60 *0.345°*	– –	– –	– –	0.58 *0.52°*	1.56% 1.56%
Sodium carboxymethyl cellulose	0.03 *0.007°*	0.03 *0.017°*	– –	– –	– –	– –	
Sodium chloride	1.00 *0.289°*	– –	– –	– –	– –	1.00 *0.52°*	0.9% 0.9%
Sodium citrate	0.32 *0.091°*	0.31 *0.178°*	0.30 *0.349°*	0.30 *0.518°*	– –	0.30 *0.52°*	3.02% 3.02%
Sodium colistimethate	0.16 *0.045°*	0.15 *0.087°*	0.14 *0.161°*	0.14 *0.235°*	0.13 *0.383°*	0.13 *0.52°*	6.85% 6.85%
Sodium folate	0.14 *0.040°*	0.12 *0.069°*	0.11 *0.120°*	0.10 *0.166°*	– –	– –	
Sodium hypophosphite	0.68 *0.190°*	0.61 *0.354°*	– –	– –	– –	– –	
Sodium iodide	0.41 *0.113°*	0.39 *0.223°*	0.39 *0.441°*	– –	– –	0.38 *0.52°*	2.37% 2.37%
Sodium lactate	0.58 *0.164°*	0.55 *0.315°*	– –	– –	– –	0.52 *0.52°*	1.72% 1.72%

Isotonic Solutions (Continued)

Chemical	Concentration of Solution, NaCl Equivalents					At Isosmotic Concentration	
	½%	1%	2%	3%	5%		
Sodium lauryl sulfate	0.10 *0.029°*	0.08 *0.046°*	0.07 *0.068°*	0.05 *0.086°*	– –	– –	
Sodium metabisulfite	0.70 *0.206°*	0.67 *0.389°*	– –	– –	– –	0.65 *0.52°*	**1.38%** **1.38%**
Sodium nitrate	0.74 *0.214°*	0.68 *0.395°*	– –	– –	– –	0.66 *0.52°*	**1.36%** **1.36%**
Sodium nitrite	0.86 *0.248°*	0.84 *0.481°*	– –	– –	– –	0.83 *0.52°*	**1.08%** **1.08%**
Sodium nitroferricyanide	0.30 *0.086°*	0.29 *0.167°*	0.28 *0.322°*	0.28 *0.475°*	– –	0.27 *0.52°*	**3.30%** **3.30%**
Sodium phosphate	0.30 *0.086°*	0.29 *0.166°*	0.28 *0.321°*	0.27 *0.471°*	– –	0.27 *0.52°*	**3.33%** **3.33%**
Sodium phosphate, dibasic ($2H_2O$)	0.44 *0.127°*	0.42 *0.244°*	0.41 *0.470°*	– –	– –	0.40 *0.52°*	**2.23%** **2.23%**
Sodium phosphate, dibasic ($12H_2O$)	0.24 *0.064°*	0.22 *0.126°*	0.21 *0.242°*	0.21 *0.358°*	– –	0.20 *0.52°*	**4.45%** **4.45%**
Sodium phosphate, exsiccated	0.56 *0.159°*	0.53 *0.306°*	– –	– –	– –	0.51 *0.52°*	**1.75%** **1.75%**
Sodium propionate	0.62 *0.177°*	0.61 *0.353°*	– –	– –	– –	0.61 *0.52°*	**1.47%** **1.47%**
Sodium ricinoleate	0.10 *0.033°*	0.10 *0.061°*	0.10 *0.112°*	0.09 *0.162°*	0.09 *0.256°*	– –	
Sodium salicylate	0.38 *0.106°*	0.36 *0.209°*	0.36 *0.412°*	– –	– –	0.36 *0.52°*	**2.53%** **2.53%**
Sodium succinate	0.32 *0.092°*	0.32 *0.184°*	0.31 *0.361°*	– –	– –	0.31 *0.52°*	**2.90%** **2.90%**
Sodium sulfate	0.28 *0.079°*	0.26 *0.148°*	0.25 *0.280°*	0.23 *0.405°*	– –	0.23 *0.52°*	**3.95%** **3.95%**
Sodium sulfate, anhydrous	0.62 *0.179°*	0.58 *0.336°*	– –	– –	– –	0.56 *0.52°*	**1.61%** **1.61%**
Sodium sulfite, exsiccated	0.72 *0.204°*	0.65 *0.375°*	– –	– –	– –	– –	
Sodium tartrate	0.33 *0.098°*	0.33 *0.193°*	0.33 *0.385°*	– –	– –	0.33 *0.52°*	**2.72%** **2.72%**
Sodium thiosulfate	0.32 *0.092°*	0.31 *0.180°*	0.31 *0.354°*	– –	– –	0.30 *0.52°*	**2.98%** **2.98%**
Sorbitol ($\frac{1}{2}H_2O$)	0.16 *0.045°*	0.16 *0.094°*	0.16 *0.191°*	0.16 *0.288°*	0.16 *0.488°*	0.16 *0.52°*	**5.48%** **5.48%**
Sparteine sulfate	0.10 *0.030°*	0.10 *0.056°*	0.10 *0.111°*	0.10 *0.167°*	0.10 *0.277°*	0.10 *0.52°*	**9.46%** **9.46%**
Spectinomycin hydrochloride	0.16 *0.045°*	0.16 *0.092°*	0.16 *0.185°*	0.16 *0.280°*	0.16 *0.460°*	0.16 *0.52°*	**5.66%** **5.66%**
Stibamine glucoside	0.16 *0.046°*	0.14 *0.079°*	0.12 *0.140°*	0.11 *0.196°*	– –	– –	
Stibophen	0.20 0.059°	0.18 *0.107°*	0.17 *0.196°*	0.16 *0.281°*	0.15 *0.435°*	– –	

Chemical	Concentration of Solution, NaCl Equivalents						
	½%	1%	2%	3%	5%	At Isosmotic Concentration	
Streptomycin calcium chloride complex	0.20 *0.057°*	0.20 *0.111°*	0.19 *0.216°*	0.19 *0.320°*	0.18 *0.520°*	0.18 *0.52°*	**5.0%** **5.0%**
Streptomycin hydrochloride	0.18 *0.050°*	0.17 *0.099°*	0.17 *0.190°*	0.16 *0.281°*	0.16 *0.460°*	– –	
Streptomycin sulfate	0.08 *0.020°*	0.07 *0.038°*	0.07 *0.072°*	0.06 *0.108°*	0.06 *0.177°*	– –	
Strychnine hydrochloride	0.20 *0.060°*	0.18 *0.099°*	0.14 *0.160°*	– –	– –	– –	
Strychnine nitrate	0.12 *0.035°*	0.12 *0.068°*	– –	– –	– –	– –	
Succinylcholine chloride	0.20 *0.059°*	0.20 *0.117°*	0.20 *0.233°*	0.20 *0.353°*	– –	0.20 *0.52°*	**4.48%** **4.48%**
Sucrose	0.08 *0.023°*	0.08 *0.047°*	0.09 *0.099°*	0.09 *0.154°*	0.09 *0.268°*	0.10 *0.52°*	**9.25%** **9.25%**
Sulfadiazine sodium	0.26 *0.073°*	0.24 *0.137°*	0.23 *0.262°*	0.22 *0.381°*	– –	0.21 *0.52°*	**4.24%** **4.24%**
Sulfamerazine sodium	0.24 *0.069°*	0.23 *0.132°*	0.22 *0.248°*	0.21 *0.361°*	– –	0.20 *0.52°*	**4.53%** **4.53%**
Sulfamethazine sodium	0.22 *0.066°*	0.21 *0.122°*	0.20 *0.225°*	0.19 *0.324°*	0.18 *0.511°*	– –	
Sulfapyridine sodium	0.26 *0.073°*	0.23 *0.133°*	0.22 *0.247°*	0.21 *0.358°*	– –	0.20 *0.52°*	**4.55%** **4.55%**
Sulfathiazole sodium	0.23 *0.067°*	0.22 *0.124°*	0.21 *0.236°*	0.20 *0.340°*	– –	0.19 *0.52°*	**4.82%** **4.82%**
Sulfisoxazole diethanolamine	0.20 *0.059°*	0.18 *0.104°*	0.16 *0.186°*	0.15 *0.262°*	– –	– –	
Sulfobromophthalein sodium	0.07 *0.019°*	0.06 *0.034°*	0.05 *0.060°*	0.05 *0.084°*	0.04 *0.123°*	– –	
Suramin sodium	0.10 *0.030°*	0.10 *0.058°*	0.10 *0.112°*	0.10 *0.169°*	0.10 *0.278°*	– –	
Synephrine tartrate	0.18 *0.048°*	0.17 *0.095°*	0.16 *0.190°*	0.16 *0.282°*	0.16 *0.453°*	0.16 *0.52°*	**5.83%** **5.83%**
Tannic acid	0.03 *0.009°*	0.03 *0.017°*	0.03 *0.034°*	0.03 *0.052°*	0.03 *0.084°*	– –	
Tartaric acid	0.26 *0.075°*	0.25 *0.144°*	0.24 *0.278°*	0.23 *0.406°*	– –	0.23 *0.52°*	**3.9%** **3.9%**
Terbutaline sulfate	0.14 *0.042°*	0.14 *0.082°*	0.14 *0.161°*	0.14 *0.238°*	0.13 *0.390°*	0.13 *0.52°*	**6.75%** **6.75%**
Tetracaine hydrochloride	0.20 *0.062°*	0.18 *0.109°*	0.17 *0.189°*	0.15 *0.261°*	0.12 *0.358°*	– –	
Tetracycline hydrochloride	0.16 *0.046°*	0.14 *0.078°*	0.12 *0.128°*	0.10 *0.172°*	– –	– –	
Tetraethylammonium bromide	0.36 *0.098°*	0.33 *0.183°*	0.30 *0.343°*	0.28 *0.493°*	– –	0.28 *0.52°*	**3.17%** **3.17%**
Tetraethylammonium chloride	0.36 *0.100°*	0.34 *0.194°*	0.33 *0.388°*	– –	– –	0.33 *0.52°*	**2.67%** **2.67%**
Tetrahydrozoline hydrochloride	0.30 *0.090°*	0.28 *0.162°*	0.25 *0.285°*	0.23 *0.406°*	– –	– –	

Isotonic Solutions (Continued)

Chemical	Concentration of Solution, NaCl Equivalents					At Isosmotic Concentration	
	½%	1%	2%	3%	5%		
Theophylline	0.10 *0.028°*	– –	– –	– –	– –	– –	
Theophylline sodium glycinate	0.32 *0.090°*	0.31 *0.180°*	0.31 *0.355°*	– –	– –	0.31 *0.52°*	**2.94%** **2.94%**
Thiamine hydrochloride	0.26 *0.074°*	0.25 *0.139°*	0.23 *0.262°*	0.22 *0.378°*	– –	0.21 *0.52°*	**4.24%** **4.24%**
Thiethylperazine maleate	0.10 *0.030°*	0.09 *0.050°*	0.08 *0.089°*	0.07 *0.119°*	0.05 *0.153°*	– –	
Thiocyanate sodium	0.71 *0.205°*	0.71 *0.410°*	– –	– –	– –	0.71 *0.52°*	**1.27%** **1.27%**
Thiopental sodium	0.28 *0.079°*	0.27 *0.155°*	0.27 *0.302°*	0.26 *0.447°*	– –	0.26 *0.52°*	**3.5%** **3.5%**
Thiopropazate dihydrochloride	0.20 *0.053°*	0.16 *0.090°*	0.12 *0.137°*	0.10 *0.170°*	0.08 *0.222°*	– –	
Thioridazine hydrochloride	0.06 *0.015°*	0.05 *0.025°*	0.04 *0.042°*	0.03 *0.055°*	0.03 *0.075°*	– –	
Thiotepa	0.16 *0.045°*	0.16 *0.090°*	0.16 *0.182°*	0.16 *0.278°*	0.16 *0.460°*	0.16 *0.52°*	**5.67%** **5.67%**
Ticarcillin disodium	0.20 *0.056°*	0.20 *0.113°*	0.20 *0.226°*	0.19 *0.339°*	– –	0.19 *0.52°*	**4.62%** **4.62%**
Timolol maleate	0.14 *0.038°*	0.13 *0.077°*	0.12 *0.146°*	– –	– –	– –	
Tobramycin	0.08 *0.019°*	0.07 *0.038°*	0.07 *0.075°*	0.07 *0.112°*	0.06 *0.187°*	– –	
Tolazoline hydrochloride	0.36 *0.107°*	0.34 *0.194°*	0.31 *0.358°*	0.30 *0.512°*	– –	0.30 *0.52°*	**3.05%** **3.05%**
Tribromoethanol	0.06 *0.015°*	0.05 *0.030°*	0.05 *0.057°*	– –	– –	– –	
Tridihexethyl chloride	0.16 *0.047°*	0.16 *0.096°*	0.16 *0.191°*	0.16 *0.280°*	0.16 *0.463°*	0.16 *0.52°*	**5.62%** **5.62%**
Triethanolamine	0.20 *0.058°*	0.21 *0.121°*	0.22 *0.252°*	0.22 *0.383°*	– –	0.22 *0.52°*	**4.05%** **4.05%**
Trifluoperazine dihydrochloride	0.18 *0.052°*	0.18 *0.100°*	– –	– –	– –	– –	
Triflupromazine hydrochloride	0.10 *0.031°*	0.09 *0.051°*	0.05 *0.061°*	0.04 *0.073°*	0.03 *0.092°*	– –	
Trimeprazine tartrate	0.10 *0.023°*	0.06 *0.035°*	0.04 *0.045°*	0.03 *0.052°*	0.02 *0.061°*	– –	
Trimethadione	0.23 *0.069°*	0.23 *0.133°*	0.22 *0.257°*	0.22 *0.378°*	– –	0.21 *0.52°*	**4.22%** **4.22%**
Trimethaphan camsylate	0.12 *0.033°*	0.10 *0.060°*	0.10 *0.111°*	0.09 *0.158°*	0.09 *0.248°*	– –	
Trimethobenzamide hydrochloride	0.12 *0.033°*	0.10 *0.062°*	0.10 *0.108°*	0.09 *0.153°*	0.08 *0.232°*	– –	
Tripelennamine hydrochloride	0.38 *0.110°*	0.30 *0.173°*	0.24 *0.268°*	0.20 *0.353°*	– –	– –	
Trisodium edetate (monohydrate)	0.29 *0.079°*	0.29 *0.158°*	0.28 *0.316°*	0.27 *0.472°*	– –	0.27 *0.52°*	**3.31%** **3.31%**

Isotonic Solutions (Continued)

Chemical	Concentration of Solution, NaCl Equivalents						
	½%	1%	2%	3%	5%	At Isosmotic Concentration	
Tromethamine	0.26 *0.075°*	0.26 *0.152°*	0.26 *0.305°*	0.26 *0.458°*	– –	0.26 *0.52°*	**3.41%** **3.41%**
Tropacocaine hydrochloride	0.30 *0.085°*	0.25 *0.143°*	0.22 *0.250°*	0.20 *0.347°*	– –	0.18 *0.52°*	**4.92%** **4.92%**
Tropicamide	0.10 *0.030°*	0.09 *0.050°*	– –	– –	– –	– –	
Trypan blue	0.26 *0.075°*	0.26 *0.150°*	– –	– –	– –	– –	
Tryparsamide	0.20 *0.057°*	0.20 *0.113°*	0.20 *0.225°*	0.20 *0.339°*	– –	0.19 *0.52°*	**4.62%** **4.62%**
Tuaminoheptane sulfate	0.28 *0.078°*	0.27 *0.154°*	0.27 *0.304°*	0.27 *0.466°*	– –	0.26 *0.52°*	**3.4%** **3.4%**
Tubocurarine chloride	0.14 *0.042°*	0.13 *0.077°*	0.11 *0.124°*	0.10 *0.175°*	0.09 *0.269°*	– –	
Urea	0.64 *0.188°*	0.59 *0.341°*	– –	– –	– –	0.55 *0.52°*	**1.63%** **1.63%**
Urethan	0.31 *0.089°*	0.31 *0.178°*	0.31 *0.355°*	– –	– –	0.31 *0.52°*	**2.93%** **2.93%**
Uridine	0.12 *0.035°*	0.12 *0.069°*	0.12 *0.138°*	0.12 *0.208°*	0.12 *0.333°*	0.11 *0.52°*	**8.18%** **8.18%**
Valethamate bromide	0.16 *0.044°*	0.15 *0.085°*	0.15 *0.168°*	0.14 *0.238°*	0.11 *0.324°*	– –	
Vancomycin hydrochloride	0.06 *0.015°*	0.05 *0.028°*	0.04 *0.049°*	0.04 *0.066°*	0.04 *0.098°*	– –	
Vinbarbital sodium	0.26 *0.074°*	0.26 *0.148°*	0.26 *0.294°*	0.25 *0.440°*	– –	0.25 *0.52°*	**3.55%** **3.55%**
Viomycin sulfate	0.08 *0.025°*	0.08 *0.047°*	0.07 *0.087°*	0.07 *0.126°*	0.07 *0.199°*	– –	
Warfarin sodium	0.18 *0.049°*	0.17 *0.095°*	0.16 *0.181°*	0.15 *0.264°*	0.15 *0.430°*	0.15 *0.52°*	**6.10%** **6.10%**
Xylometazoline hydrochloride	0.22 *0.065°*	0.21 *0.121°*	0.20 *0.232°*	0.20 *0.312°*	– –	0.19 *0.52°*	**4.68%** **4.68%**
Zinc chloride	0.66 *0.190°*	0.61 *0.354°*	– –	– –	– –	– –	
Zinc *p*-phenosulfonate	0.18 *0.053°*	0.18 *0.102°*	0.18 *0.199°*	0.17 *0.295°*	0.17 *0.483°*	– –	
Zinc sulfanilate	0.22 *0.066°*	0.21 *0.120°*	0.20 *0.226°*	0.19 *0.323°*	0.18 *0.512°*	– –	
Zinc sulfate	0.16 *0.045°*	0.15 *0.085°*	0.14 *0.157°*	0.13 *0.226°*	0.12 *0.355°*	0.12 *0.52°*	**7.65%** **7.65%**
Zinc sulfate, dried	0.24 *0.072°*	0.23 *0.136°*	0.22 *0.252°*	0.21 *0.362°*	– –	0.20 *0.52°*	**4.52%** **4.52%**

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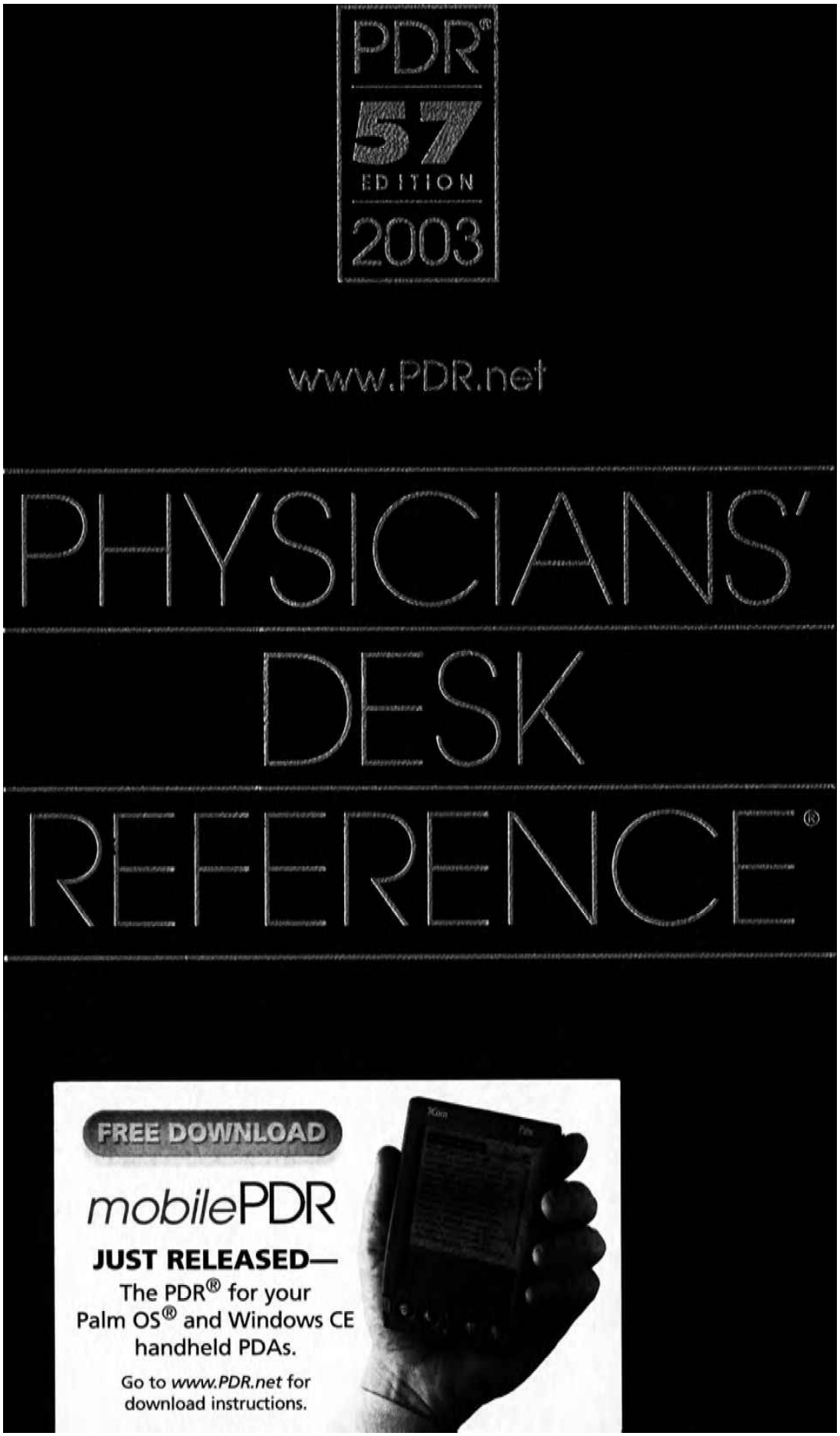
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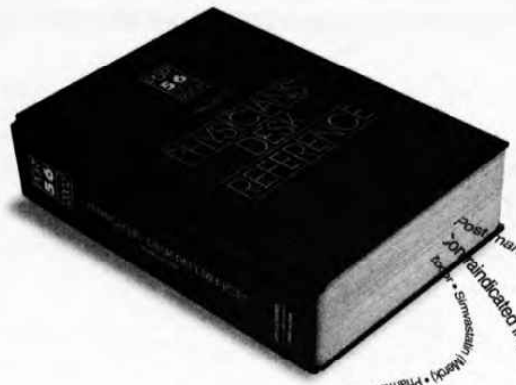

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- **Generic Availability Guide** shows which forms and strengths of a brand-name drug are also available generically.
- **Imprint Identification Guide** enables you to establish the nature of any unknown tablet or capsule by matching its imprint against an exhaustive catalog of identifying codes.

The *PDR Companion Guide* includes all drugs described in *PDR, PDR for Nonprescription Drugs and Dietary Supplements™,* and *PDR for Ophthalmic Medicines™.* We're certain that you'll find it makes safe, appropriate selection of drugs faster and easier than ever before.

PDR and its major companion volumes are also found in the **PDR® Electronic Library™** on CD-ROM, now used in over 100,000 practices. This Windows-compatible disc provides users with a complete database of *PDR* prescribing information, electronically searchable for instant retrieval. A standard subscription includes *PDR's* sophisticated search software and an extensive file of chemical structures, illustrations, and full-color product photographs. Optional enhancements include the complete contents of *The Merck Manual Seventeenth Edition, Stedman's Medical Dictionary, and Stedman's Spellchecker.* For anyone who wants to run a fast double check on a proposed prescription, there's also the *PDR® Drug Interactions and Side Effects System™* — sophisticated software capable of automatically screening a 20-drug regimen for conflicts, then proposing alternatives for any problematic medication. This unique decision-making tool now comes free with the *PDR Electronic Library.*

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A Fond Farewell

With this edition, the publishers of *PDR* bid goodbye and good wishes to the editor, Dave Sifton, who for the past two decades has been writing and managing the editorial sections of *PDR* and its family of products. Over the past 15 years, Dave has played an instrumental role in the development of many of the new products introduced by *PDR* to help practitioners in their daily prescribing. These products include *PDR's* first venture into electronic publishing, the 1988 edition of *PDR on CD-ROM,* and *PDR's* first handheld electronic drug database, *Pocket PDR.* Dave helped launch the forerunner to the *PDR Companion Guide,* and in the '90s, he created a series of *PDR Family Guides* to provide consumers with plain-spoken information on healthcare and drugs, many of which remain available today, both in print and on the Web. Dave retires at the beginning of 2003. We extend to him our sincere appreciation for an extraordinary contribution, and wish him the best in the years ahead.

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www.pharmacy.arizona.edu

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Fax: 501-686-7357

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Drug Information Center
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www.aahs.org

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School of Pharmacy
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Baltimore, MD 21201
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Fax: 410-706-0754
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Drug Information Service
National Institutes of Health
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Drug Information
Pharmacy Dept.
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Easton, MD 21601
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Boston, MA 02115
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Drug Information Center
UMass Memorial Healthcare Hospital
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508-856-2775 (24 hour)
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University of Michigan Health System
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Ann Arbor, MI 48109-0008
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Fax: 734-936-7027
www.pharm.med.edu/public

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Drug Information Center
Department of Pharmacy Services
Detroit Receiving Hospital and University Health Center
4201 St. Antoine Blvd.
Detroit, MI 48201
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Fax: 313-993-2522
www.dmcpharmacy.org

LANSING

Drug Information Services
Sparrow Hospital
1215 East Michigan Ave.
Lansing, MI 48912
7 days/week, 24 hours
517-364-2444
Fax: 517-364-2088

PONTIAC

Drug Information Center
St. Joseph Mercy Hospital
44405 Woodward Ave.
Pontiac, MI 48341
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248-858-3055
Fax: 248-858-3010

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Drug Information Services
William Beaumont Hospital
3601 West 13 Mile Rd.
Royal Oak, MI 48073-6769
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Fax: 248-551-3301

SOUTHFIELD

Drug Information Service
Providence Hospital
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Southfield, MI 48075
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248-849-3125
Fax: 248-849-5364

MISSISSIPPI

JACKSON

Drug Information Center
University of Mississippi Medical Center
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Jackson, MS 39216
Mon.-Fri. 8 AM-4:30 PM
601-984-2060
Fax: 601-984-2064

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KANSAS CITY

University of Missouri-Kansas City
Drug Information Center
2411 Holmes St., MG-200
Kansas City, MO 64108-2792
Mon.-Fri. 8 AM-5 PM
816-235-5490
Fax: 816-235-5491
www.umkc.edu/druginfo

SPRINGFIELD

Drug Information Center
St. Johns Regional Health Center
1235 E. Cherokee St.
Springfield, MO 65804
Mon.-Fri. 7:30 AM-4:30 PM
417-885-3488
Fax: 417-888-7788
E-mail: tbarks@sprg.smhs.com

ST. JOSEPH

Drug Information Service
Heartland Hospital West
801 Faraon St.
St. Joseph, MO 64501
Mon.-Fri. 9 AM-5:30 PM
816-271-7582
Fax: 816-271-7590

MONTANA

MISSOULA

Drug Information Service
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E-mail: druginfo@selway.umt.edu

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OMAHA

Drug Informatics Service
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2500 California Plaza
Omaha, NE 68178
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402-280-5101
Fax: 402-280-5149
www.druginfo.creighton.edu

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NEWARK

New Jersey Poison Information and Education System
65 Bergen St.
Newark, NJ 07107
7 days/week, 24 hours
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800-222-1222
(poison control)
Fax: 973-643-2679
www.njpies.org
E-mail: bruck@njpies.org

NEW BRUNSWICK

Drug Information Service
Robert Wood Johnson University Hospital
Pharmacy Department
1 Robert Wood Johnson Pl.
New Brunswick, NJ 08901
Mon.-Fri. 8:30 AM-4:30 PM
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Fax: 732-937-8584

NEW MEXICO

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New Mexico Poison & Drug Information Center
University of New Mexico Health Sciences Center
Albuquerque, NM 87131
7 days/week, 24 hours
505-272-2222
800-222-1222 (NM only)
Fax: 505-272-5892
http://hsc.unm.edu/pharmacy/poison

NEW YORK

BROOKLYN

International Drug Information Center
Long Island University
Arnold & Marie Schwartz College of Pharmacy & Health Sciences
1 University Plaza
RM-HS509
75 Dekalb Ave.
Brooklyn, NY 11201
Mon.-Fri. 9 AM-5 PM
718-488-1064
Fax: 718-780-4056
www.liu.edu

Drug Information Center
Brookdale University Hospital and Medical Center
1 Brookdale Plaza
Brooklyn, NY 11212
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Fax: 718-240-6606

COOPERSTOWN

Drug Information Center
Bassett Healthcare
1 Atwell Rd.
Cooperstown, NY 13326
7 days/week, 24 hours
607-547-3686
Fax: 607-547-3629

NEW HYDE PARK

Drug Information Center
St. Johns University at Long Island Jewish Medical Center
270-05 76th Ave.
New Hyde Park, NY 11040
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Fax: 212-639-2171

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1 Gustave Levy Pl.
New York, NY 10029
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212-241-6619
Fax: 212-348-7927

Drug Information Service
New York Presbyterian Hospital
Room K04
525 E. 68th St.
New York, NY 10021
Mon.-Fri. 9 AM-5 PM
212-746-0741
Fax: 212-746-4434

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Drug Information Center
Mercy Medical Center
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Rockville Center, NY 11570
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516-705-1053
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Drug Information Service Center
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OHIO

ADA

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Raabe College of Pharmacy
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419-772-2307
Fax: 419-772-2289
www.onu.edu/pharmacy/druginfo

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Mon.-Fri. 8:30 AM-4:30 PM
216-444-6456
(for healthcare professionals only)
Fax: 216-444-6157

COLUMBUS

Drug Information Center
Ohio State University Hospital
Dept. of Pharmacy
Doan Hall 368
410 W. 10th Ave.
Columbus, OH 43210-1228
Mon.-Fri. 8 AM-4 PM
614-293-8679
Fax: 614-293-3264
E-mail: visconti-1@medctr.osu.edu

Drug Information Center
Riverside Methodist Hospital
3535 Olentangy River Road
Columbus, OH 43214
Mon.-Fri. 8:30 AM-4 PM
614-566-5425
Fax: 614-566-5850

TOLEDO

Drug Information Services
St. Vincent Mercy Medical Center
2213 Cherry St.
Toledo, Ohio 43608-2691
Mon.-Fri. 8 AM-4 PM
419-251-4227
Fax: 419-251-3662
www.rx.medctr.ohio-state.edu

OKLAHOMA

OKLAHOMA CITY

Drug Information Service
Integris Health
3300 Northwest Expressway
Oklahoma City, OK 73112
Mon.-Fri. 8 AM-4:30 PM
405-949-3660
Fax: 405-951-8274

Drug Information Center
OU Medical Center Presbyterian Tower
700 NE 13th St.
Oklahoma City, OK 73104
Mon.-Fri. 8 AM-4:30 PM
405-271-6226
Fax: 405-271-6281

TULSA

Drug Information Center
Saint Francis Hospital
6161 S. Yale Ave.
Tulsa, OK 74136
Mon.-Fri. 8 AM-4 PM
918-494-6339
(for healthcare professionals only)
Fax: 918-494-1893

PENNSYLVANIA

PHILADELPHIA

Drug Information Center
Temple University Hospital
Dept. of Pharmacy
3401 N. Broad St.
Philadelphia, PA 19140
Mon.-Fri. 8 AM-4:30 PM
215-707-4644
Fax: 215-707-3463

Drug Information Service
Tenet Health System Hahnemann University Hospital
Department of Pharmacy
MS 451
Broad and Vine Streets
Philadelphia, PA 19102
Mon.-Fri. 8 AM-4 PM
215-762-DRUG (3784)
(for healthcare professionals only)
Fax: 215-762-7993

Drug Information Service
Dept. of Pharmacy
Thomas Jefferson University Hospital
111 S. 11th St.
Philadelphia, PA 19107-5098
Mon.-Fri. 8 AM-5 PM
215-955-8877
Fax: 215-923-3316

University of Pennsylvania Health System Drug Information Service
Hospital of the University of Pennsylvania
Department of Pharmacy
3400 Spruce St.
Philadelphia, PA 19104
Mon.-Fri. 8:30 AM-4 PM
215-662-2903
Fax: 215-662-4319

PITTSBURGH

The Christopher and Nicole Browett Pharmaceutical Information Center
Mylan School of Pharmacy
Duquesne University
431 Mellon Hall
Pittsburgh, PA 15282
Mon.-Fri. 8 AM-4 PM
412-396-4600
Fax: 412-396-4488

Drug Information Center
University of Pittsburgh
137 Victoria Hall
200 Lothrop St.
Pittsburgh, PA 15261
Mon.-Fri. 8:30 AM-4:30 PM
412-624-3784
(for healthcare professionals only)
Fax: 412-624-6350
E-mail: druginfo@msx.upmc.edu

UPLAND

Drug Information Center
Crozer-Chester Medical Center
Dept. of Pharmacy
1 Medical Center Blvd.
Upland, PA 19013
Mon.-Fri. 8 AM-4:30 PM
610-447-2851
610-447-2862
(after hours)
(both numbers are for healthcare professionals only)
Fax: 610-447-2820

WILLIAMSPORT

Drug Information
Pharmacy Dept.
Susquehanna Health System
Rural Avenue Campus
Williamsport, PA 17701
7 days/week, 5 AM-Midnight
570-321-3083
Fax: 570-321-3230

PUERTO RICO

PONCE

Centro Informacion Medicamentos
Escuela de Medicina de Ponce
P.O. Box 7004
Ponce, PR 00732-7004
Mon.-Fri. 8 AM-4:30 PM
787-259-7085
(Spanish and English)
787-840-2575
(switchboard)
Fax: 787-842-0461

SAN JUAN

Centro de Informacion de Medicamentos-CIM
Escuela de Farmacia-RCM
P.O. Box 365067
San Juan, PR 00936-5067
Mon.-Fri. 8 AM-4:30 PM
787-758-2525, ext. 1516
Fax: 787-763-0196
E-mail: cimrcm@rcm.upr.edu

SOUTH CAROLINA

CHARLESTON

Drug Information Service
Medical University of South Carolina
150 Ashley Ave.
Rutledge Tower
Annex, Room 604
P.O. Box 250584
Charleston, SC 29425-0810
Mon.-Fri. 9 AM-5:30 PM
843-792-3896
800-922-5250
Fax: 843-792-5532

COLUMBIA

Drug Information Service
University of South Carolina
College of Pharmacy
University of South Carolina
Columbia, SC 29208
Mon.-Fri. 8 AM-Midnight
803-777-7804
Fax: 803-777-6127
www.pharm.sc.edu

SPARTANBURG

Drug Information Center
Spartanburg Regional Medical Center
101 E. Wood St.
Spartanburg, SC 29303
Mon.-Fri. 8 AM-5 PM
864-560-6910
Fax: 864-560-7323

TENNESSEE

KNOXVILLE

Drug Information Center
University of Tennessee Medical Center at Knoxville
1924 Alcoa Highway
Knoxville, TN 37920-6999
Mon.-Fri. 8 AM-4:30 PM
865-544-9124
Fax: 865-525-0326
865-544-8242

MEMPHIS

South East Regional Drug Information Center
VA Medical Center
1030 Jefferson Ave.
Memphis, TN 38104
Mon.-Fri. 6:30 AM-3 PM
901-523-8990, ext. 6720
Fax: 901-577-7306

Drug Information Center
University of Tennessee
875 Monroe Ave.
Suite 116
Memphis, TN 38163
Mon.-Fri. 7 AM-7 PM
901-448-5555
Fax: 901-448-5419
E-mail: utdic@utmem.edu

TEXAS

AMARILLO

Drug Information Center
Texas Tech University School of Pharmacy
1300 Coulter Rd.
Amarillo, TX 79106
Mon.-Fri. 8 AM-5 PM
806-356-4008
(for healthcare professionals only)
Fax: 806-356-4017

GALVESTON

Drug Information Center
University of Texas Medical Branch
301 University Blvd. - G01
Galveston, TX 77555-0701
Mon.-Fri. 8 AM-5 PM
409-772-2734
Fax: 409-747-5222

HOUSTON

Drug Information Center
Ben Taub General Hospital
Texas Southern University/HCHD
1504 Taub Loop
Houston, TX 77030
Mon.-Fri. 8 AM-5 PM
713-873-3710
Fax: 713-873-3711

LACKLAND A.F.B.

Drug Information Center
Dept. of Pharmacy
Wilford Hall Medical Center
2200 Berquist Dr.
Suite 1
Lackland A.F.B., TX 78236
7 days/week, 24 hours
210-292-5414
Fax: 210-292-3722

LUBBOCK

Drug Information and Consultation Service
Covenant Medical Center
3615 19th St.
Lubbock, TX 79410
Mon.-Fri. 8 AM-5 PM
806-725-0408
Fax: 806-725-0305

SAN ANTONIO

Drug Information Service
University of Texas Health Science Center at San Antonio
Department of Pharmacology
7703 Floyd Curl Drive
San Antonio, TX 78229-3900
Mon.-Fri. 8 AM-4 PM
210-567-4280
Fax: 210-567-4305

TEMPLE

Drug Information Center
Scott and White Memorial Hospital
2401 S. 31st St.
Temple, TX 76508
Mon.-Fri. 8 AM-6 PM
254-724-4636
Fax: 254-724-1731

UTAH

SALT LAKE CITY

Drug Information Service
University of Utah Hospital
Dept. of Pharmacy Services
Room A-050
50 N. Medical Dr.
Salt Lake City, UT 84132
Mon.-Fri. 8:30 AM-4:30 PM
801-581-2073
Fax: 801-585-6688
E-mail: drug.info@hsc.utah.edu

VIRGINIA

HAMPTON

Drug Information Service
Hampton University School of Pharmacy
Kittrell Hall Room 208
Hampton, VA 23668
Mon.-Fri. 8 AM-5 PM
757-728-6687
757-728-6693
(drug info hotline)
Fax: 757-727-5840
E-mail: druginfo@hamptonu.edu

WEST VIRGINIA

MORGANTOWN

West Virginia Drug Information Center
WV University-Robert C. Byrd Health Sciences Center
1124 HSN, P.O. Box 9550
Morgantown, WV 26506
Mon.-Fri. 8:30 AM-5 PM
304-293-6640
800-352-2501 (WV)
Fax: 304-293-7672

WYOMING

LARAMIE

Drug Information Center
University of Wyoming
P.O. Box 3375
Laramie, WY 82071
Mon.-Fri. 8 AM-5 PM
307-766-6988
E-mail: rxinfo@uwyo.edu

Moban—Cont.

cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Drug Interactions

Potentiation of drugs administered concurrently with MOBAN has not been reported. Additionally, animal studies have not shown increased toxicity when MOBAN is given concurrently with representative members of three classes of drugs (i.e., barbiturates, chloral hydrate and antiparkinson drugs).

ADVERSE REACTIONS

CNS EFFECTS

The most frequently occurring effect is initial drowsiness that generally subsides with continued usage of the drug or lowering of the dose.

Noted less frequently were depression, hyperactivity and euphoria.

Neurological

Extrapyramidal Reactions

Extrapyramidal reactions noted below may occur in susceptible individuals and are usually reversible with appropriate management.

Akathisia

Motor restlessness may occur early.

Parkinson Syndrome

Akinesia, characterized by rigidity, immobility and reduction of voluntary movements and tremor, have been observed. Occurrence is less frequent than akathisia.

Dystonic Syndrome

Prolonged abnormal contractions of muscle groups occur infrequently. These symptoms may be managed by the addition of a synthetic antiparkinson agent (other than L-dopa), small doses of sedative drugs, and/or reduction in dosage.

Tardive Dyskinesia

Antipsychotic drugs are known to cause a syndrome of dyskinetic movements commonly referred to as tardive dyskinesia. The movements may appear during treatment or upon withdrawal of treatment and may be either reversible or irreversible (i.e., persistent) upon cessation of further neuroleptic administration.

The syndrome is known to have a variable latency for development and the duration of the latency cannot be determined reliably. It is thus wise to assume that any antipsychotic agent has the capacity to induce the syndrome and act accordingly until sufficient data has been collected to settle the issue definitively for a specific drug product. In the case of antipsychotic known to produce the irreversible syndrome, the following has been observed.

Tardive dyskinesia has appeared in some patients on long-term therapy and has also appeared after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). There may be involuntary movements of extremities.

There is no known effective treatment of tardive dyskinesia; antiparkinsonism agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, the syndrome may be masked. It has been reported that fine vermicular movements of the tongue may be an early sign of the syndrome and if the medication is stopped at that time the syndrome may not develop (See WARNINGS).

Autonomic Nervous System

Occasionally blurring of vision, tachycardia, nausea, dry mouth and salivation have been reported. Urinary retention and constipation may occur particularly if anticholinergic drugs are used to treat extrapyramidal symptoms. One patient being treated with MOBAN (molindone hydrochloride) experienced priapism which required surgical intervention, apparently resulting in residual impairment of erectile function.

Laboratory Tests

There have been rare reports of leucopenia and leucocytosis. If such reactions occur, treatment with MOBAN may continue if clinical symptoms are absent. Alterations of blood glucose, B.U.N., and red blood cells have not been considered clinically significant.

Metabolic and Endocrine Effects

Alteration of thyroid function has not been significant. Amenorrhea has been reported infrequently. Resumption of menses in previously amenorrheic women has been reported. Initially heavy menses may occur. Galactorrhea and gynecomastia have been reported infrequently. Increase in libido has been noted in some patients. Impotence has not been reported. Although both weight gain and weight loss have been in the direction of normal or ideal weight, excessive weight gain has not occurred with MOBAN.

Hepatic Effects

There have been rare reports of clinically significant alterations in liver function in association with MOBAN use.

Cardiovascular

Rare, transient, non-specific T wave changes have been reported on E.K.G. Association with a clinical syndrome has not been established. Rarely has significant hypotension been reported.

Ophthalmological

Lens opacities and pigmentary retinopathy have not been reported where patients have received MOBAN. In some patients, phenothiazine induced lenticular opacities have resolved following discontinuation of the phenothiazine while continuing therapy with MOBAN.

Skin

Early, non-specific skin rash, probably of allergic origin, has occasionally been reported. Skin pigmentation has not been seen with MOBAN usage alone.

MOBAN has certain pharmacological similarities to other antipsychotic agents. Because adverse reactions are often extensions of the pharmacological activity of a drug, all of the known pharmacological effects associated with other antipsychotic drugs should be kept in mind when MOBAN is used. Upon abrupt withdrawal after prolonged high dosage an abstinence syndrome has not been noted.

OVERDOSAGE

Symptomatic, supportive therapy should be the rule.

Gastric lavage is indicated for the reduction of absorption of MOBAN which is freely soluble in water.

Since the adsorption of MOBAN by activated charcoal has not been determined, the use of this antidote must be considered of theoretical value.

Emesis in a comatose patient is contraindicated. Additionally, while the emetic effect of apomorphine is blocked by MOBAN in animals, this blocking effect has not been determined in humans.

A significant increase in the rate of removal of unmetabolized MOBAN from the body by forced diuresis, peritoneal or renal dialysis would not be expected. (Only 2% of a single ingested dose of MOBAN is excreted unmetabolized in the urine). However, poor response of the patient may justify use of these procedures.

While the use of laxatives or enemas might be based on general principles, the amount of unmetabolized MOBAN in feces is less than 1%. Extrapyramidal symptoms have responded to the use of diphenhydramine (Benadryl*), Amantadine HCl (Symmetrel®*) and the synthetic anticholinergic antiparkinson agents, (i.e., Artane*, Cogentin*, Akineton*).

DOSAGE AND ADMINISTRATION

Initial and maintenance doses of MOBAN (molindone hydrochloride) should be individualized.

Initial Dosage Schedule

The usual starting dosage is 50–75 mg/day.

— Increase to 100 mg/day in 3 or 4 days.

— Based on severity of symptomatology, dosage may be titrated up or down depending on individual patient response.

— An increase to 225 mg/day may be required in patients with severe symptomatology.

Elderly and debilitated patients should be started on lower dosage.

Maintenance Dosage Schedule

1. Mild-5 mg-15 mg three or four times a day.
2. Moderate-10 mg-25 mg three or four times a day.
3. Severe-225 mg/day may be required.

HOW SUPPLIED

As tablets in bottles of 100 with potencies and colors as follows:

[See table at top of previous page]

As a concentrate (clear, colorless to straw-yellow syrup) containing 20 mg molindone hydrochloride per mL in 4 oz. (120 mL) bottles, NDC 63481-460-04.

Store at controlled room temperature 15°–30°C (59°–86°F). Protect from light.

*Benadryl-Trademark, Warner-Lambert.

*Symmetrel-Trademark, Endo Pharmaceuticals Inc.

*Artane-Trademark, Lederle Laboratories

*Cogentin-Trademark, Merck & Co., Inc.

*Akineton-Trademark, Knoll Laboratories.

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6500-01/December, 2000

Shown in Product Identification Guide, page 312

NARCAN® ℞

[nar'kan]

(Naloxone Hydrochloride Injection, USP)

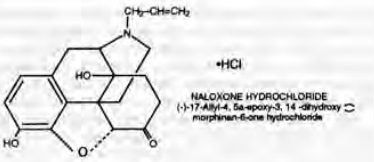
Opioid Antagonist

DESCRIPTION

NARCAN (naloxone hydrochloride injection, USP), an opioid antagonist, is a synthetic congener of oxymorphone. In structure it differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by an allyl group.

[See chemical structure at top of next column]

Naloxone hydrochloride occurs as a white to slightly off-white powder, and is soluble in water, in dilute acids, and in



NALOXONE HYDROCHLORIDE
(-)-17-Allyl-4, 5α-epoxy-3, 14 -dihydroxy morphinan-6-one hydrochloride

strong alkali; slightly soluble in alcohol; practically insoluble in ether and in chloroform.

NARCAN injection is available as a sterile solution for intravenous, intramuscular and subcutaneous administration in three concentrations: 0.02 mg, 0.4 mg and 1 mg of naloxone hydrochloride per mL. pH is adjusted to 3.5 ± 0.5 with hydrochloric acid.

The 0.02 mg/mL strength is a paraben-free formulation containing 9 mg/mL sodium chloride.

The 0.4 mg/mL vial contains 8.6 mg/mL of sodium chloride and 2 mg/mL of methylparaben and propylparaben as preservatives in a ratio of 9:1. The 0.4 mg/mL ampul is available in a paraben-free formulation containing 9 mg/mL of sodium chloride.

The 1 mg/mL vial contains 8.35 mg/mL of sodium chloride and 2 mg/mL of methylparaben and propylparaben as preservatives in a ratio of 9:1. The 1 mg/mL ampul is available in a paraben-free formulation containing 9 mg/mL of sodium chloride.

CLINICAL PHARMACOLOGY

Complete or Partial Reversal of Opioid Depression

NARCAN prevents or reverses the effects of opioids including respiratory depression, sedation and hypotension. Also, it can reverse the psychotomimetic and dysphoric effects of agonist-antagonists such as pentazocine.

NARCAN is an essentially pure opioid antagonist, i.e., it does not possess the "agonistic" or morphine-like properties characteristic of other opioid antagonists; NARCAN does not produce respiratory depression, psychotomimetic effects or pupillary constriction. In the absence of opioids or agonistic effects of other opioid antagonists, it exhibits essentially no pharmacologic activity.

NARCAN has not been shown to produce tolerance or cause physical or psychological dependence.

In the presence of physical dependence on opioids NARCAN will produce withdrawal symptoms.

While the mechanism of action of NARCAN is not fully understood, the preponderance of evidence suggests that NARCAN antagonizes opioid effects by competing for the same receptor sites.

When NARCAN is administered intravenously, the onset of action is generally apparent within two minutes; the onset of action is only slightly less rapid when it is administered subcutaneously or intramuscularly. The duration of action is dependent upon the dose and route of administration of NARCAN. Intramuscular administration produces a more prolonged effect than intravenous administration. The requirement for repeat doses of NARCAN, however, will also be dependent upon the amount, type and route of administration of the opioid being antagonized.

Following parenteral administration, NARCAN is rapidly distributed in the body. It is metabolized in the liver, primarily by glucuronide conjugation and excreted in urine. In one study the serum half-life in adults ranged from 30 to 81 minutes (mean 64 ± 12 minutes). In a neonatal study the mean plasma half-life was observed to be 3.1 ± 0.5 hours.

Adjunctive Use in Septic Shock

Although the mechanism of action is not completely understood, NARCAN appears to block endorphin-mediated hypotension in septic shock patients.

NARCAN has been shown in some cases of septic shock to produce a rise in blood pressure that may last up to several hours; however, this pressor response has not been demonstrated to improve patient survival.

Patients who have responded to NARCAN received the drug early in the course of treatment of septic shock. Because of the limited number of patients who have been treated, optimal dosage and treatment regimens have not been established. Published reports demonstrating a pressor effect have evaluated single bolus injections of 0.4 mg over three (3) to five (5) minutes, which have been repeated for 3–5 doses depending on the response. Bolus infusion doses ranging from 0.03 mg/kg to 0.2 mg/kg over five (5) minutes have also been reported. If a response was elicited, treatment was continued by intravenous infusion of concentrations of 0.03 mg/kg/hour to 0.3 mg/kg/hour for 1–24 hours or more depending upon the clinical response.

INDICATIONS AND USAGE

NARCAN is indicated for the complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids, including propoxyphene, methadone and certain mixed agonist-antagonist analgesics: nalbuphine, pentazocine and butorphanol. NARCAN is also indicated for the diagnosis of suspected opioid tolerance or acute opioid overdosage.

NARCAN may be useful as an adjunctive agent to increase blood pressure in the management of septic shock (see **CLINICAL PHARMACOLOGY; Adjunctive Use in Septic Shock**).

CONTRAINDICATIONS

NARCAN is contraindicated in patients known to be hypersensitive to naloxone hydrochloride or to any of the other ingredients in NARCAN.

WARNINGS

NARCAN should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of opioid effects may precipitate an acute withdrawal syndrome.

The signs and symptoms of opioid withdrawal in a patient physically dependent on opioids may include, but are not limited to, the following: body aches, diarrhea, tachycardia, fever, runny nose, sneezing, piloerection, sweating, yawning, nausea or vomiting, nervousness, restlessness or irritability, shivering or trembling, abdominal cramps, weakness, and increased blood pressure. In the neonate, opioid withdrawal may also include: convulsions, excessive crying, and hyperactive reflexes.

The patient who has satisfactorily responded to NARCAN should be kept under continued surveillance and repeated doses of NARCAN should be administered, as necessary, since the duration of action of some opioids may exceed that of NARCAN.

NARCAN is not effective against respiratory depression due to non-opioid drugs. Reversal of buprenorphine-induced respiratory depression may be incomplete. If an incomplete response occurs, respirations should be mechanically assisted.

PRECAUTIONS

General

In addition to NARCAN, other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents should be available and employed when necessary to counteract acute opioid poisoning.

Abrupt postoperative reversal of opioid depression may result in nausea, vomiting, sweating, tremulousness, tachycardia, increased blood pressure, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest which may result in death.

Several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest have been reported in postoperative patients. Death, coma, and encephalopathy have been reported as sequelae of these events. These have occurred in patients most of whom had pre-existing cardiovascular disorders or received other drugs which may have similar adverse cardiovascular effects. Although a direct cause and effect relationship has not been established, NARCAN should be used with caution in patients with pre-existing cardiac disease or patients who have received medications with potential adverse cardiovascular effects, such as hypotension, ventricular tachycardia or fibrillation, and pulmonary edema. It has been suggested that the pathogenesis of pulmonary edema associated with the use of NARCAN is similar to neurogenic pulmonary edema, i.e., a centrally mediated massive catecholamine response leading to a dramatic shift of blood volume into the pulmonary vascular bed resulting in increased hydrostatic pressures.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies in animals to assess the carcinogenic potential of NARCAN have not been conducted. NARCAN was weakly positive in the Ames mutagenicity and *in vitro* human lymphocyte chromosome aberration tests and was negative in the *in vitro* Chinese hamster V79 cell HGPRT mutagenicity assay and in an *in vivo* rat bone marrow chromosome aberration study. Reproduction studies conducted in mice and rats at doses as high as 50 times the usual human dose (10 mg/day) demonstrated no impairment of fertility.

Use in Pregnancy

Teratogenic Effects Pregnancy Category B: Reproduction studies performed in mice and rats at doses as high as 50 times the usual human dose (10 mg/day), revealed no evidence of impaired fertility or harm to the fetus due to NARCAN. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, NARCAN should be used during pregnancy only if clearly needed.

Non-teratogenic Effects: Risk-benefit must be considered before NARCAN is administered to a pregnant woman who is known or suspected to be opioid-dependent since maternal dependence may often be accompanied by fetal dependence. Naloxone crosses the placenta and may precipitate withdrawal in the fetus as well as in the mother.

Use in Labor and Delivery

It is not known if NARCAN affects the duration of labor and/or delivery.

Nursing Mothers

It is not known whether NARCAN is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NARCAN is administered to a nursing woman.

Usage in Pediatric Patients and Neonates for Septic Shock

The safety and effectiveness of NARCAN in the treatment of hypotension in pediatric patients and neonates with septic shock have not been established.

Renal Insufficiency/Failure

The safety and effectiveness of NARCAN in patients with renal insufficiency/failure have not been established in well-controlled clinical trials. Caution should be exercised when NARCAN is administered to this patient population.

0.4 mg/mL	10 mL multiple dose vial-box of 1	NDC 63481-365-05
0.4 mg/mL (paraben-free)	1 mL ampul-box of 10	NDC 63481-358-10
1 mg/mL	10 mL multiple dose vial-box of 1	NDC 63481-368-05
1 mg/mL (paraben-free)	2 mL ampul-box of 10	NDC 63481-377-10
0.02 mg/mL (paraben-free)	2 mL ampul-box of 10	NDC 63481-359-10

Liver Disease

The safety and effectiveness of NARCAN in patients with liver disease have not been established in well-controlled clinical trials. In one small study in patients with liver cirrhosis, plasma naloxone concentrations were approximately six times higher than in patients without liver disease. NARCAN was well tolerated and no adverse events were reported. Caution should be exercised when NARCAN is administered to patients with liver disease.

ADVERSE REACTIONS

Postoperative

The following adverse events have been associated with the use of NARCAN (naloxone hydrochloride injection, USP) in postoperative patients: hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. Excessive doses of NARCAN in postoperative patients may result in significant reversal of analgesia and may cause agitation (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION; Usage in Adults; Postoperative Opioid Depression**).

Opioid Depression

Abrupt reversal of opioid depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, tremulousness, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest which may result in death (see **PRECAUTIONS**).

Opioid Dependence

Abrupt reversal of opioid effects in persons who are physically dependent on opioids may precipitate an acute withdrawal syndrome which may include, but is not limited to, the following signs and symptoms: body aches, fever, sweating, runny nose, sneezing, piloerection, yawning, weakness, shivering or trembling, nervousness, restlessness or irritability, diarrhea, nausea or vomiting, abdominal cramps, increased blood pressure, tachycardia. In the neonate, opioid withdrawal may also include: convulsions; excessive crying; hyperactive reflexes (see **WARNINGS**).

Agitation and paresthesias have been infrequently reported with the use of NARCAN.

DRUG ABUSE AND DEPENDENCE

NARCAN is an opioid antagonist. Physical dependence associated with the use of NARCAN has not been reported. Tolerance to the opioid antagonist effect of NARCAN is not known to occur.

OVERDOSAGE

There is limited clinical experience with NARCAN overdosage in humans.

Adult Patients

In one study, volunteers and morphine-dependent subjects who received 24 mg/70 kg did not demonstrate toxicity.

In another study, 36 patients with acute stroke received a loading dose of 4 mg/kg (10 mg/m^2/min) of NARCAN followed immediately by 2 mg/kg/hr for 24 hours. There were a few reports of serious adverse events: seizures (2 patients), severe hypertension (1), and hypotension and/or bradycardia (3).

At doses of 2 mg/kg in normal subjects, memory impairment has been reported.

Pediatric Patients

Up to 11 doses of 0.2 mg of naloxone (2.2 mg) have been administered to children following overdose of diphenoxylate hydrochloride with atropine sulfate. Pediatric reports include a 2-1/2 year-old child who inadvertently received a dose of 20 mg of naloxone and a 4-1/2 year-old child who received 11 doses during a 12-hour period, both of whom had no adverse sequelae.

Patient Management

Patients who experience a NARCAN overdose should be treated symptomatically in a closely supervised environment. Physicians should contact a poison control center for the most up-to-date patient management information.

Animal Data

The intravenous single-dose LD_{50} (95% confidence limits) in rats and mice is 150 (135–165) mg/kg and 109 (97–121) mg/kg, respectively. In newborn rats, the subcutaneous single-dose LD_{50} (95% confidence limits) is 260 (228–296) mg/kg. Subcutaneous injection in rats at 100 mg/kg/day for three weeks produced only transiently increased salivation and partial ptosis; no drug-related effects were seen at 10 mg/kg/day for three weeks.

Some chemical impurities in naloxone, i.e., noroxymorphone and bisnaloxone, have been shown to produce emesis in dogs when administered alone at I.V. doses equivalent to impurity levels present in naloxone at 60 times the usual human dose (10 mg/day).

DOSAGE AND ADMINISTRATION

NARCAN may be administered intravenously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved by intravenous administration, which is recommended in emergency situations.

Since the duration of action of some opioids may exceed that of NARCAN, the patient should be kept under continued surveillance. Repeated doses of NARCAN should be administered, as necessary.

Intravenous Infusion

NARCAN may be diluted for intravenous infusion in normal saline or 5% dextrose-solutions. The addition of 2 mg of NARCAN in 500 mL of either solution provides a concentration of 0.004 mg/mL. Mixtures should be used within 24 hours. After 24 hours, the remaining unused mixture must be discarded. The rate of administration should be titrated in accordance with the patient's response.

NARCAN should not be mixed with preparations containing bisulfite, metabisulfite, long-chain or high molecular weight anions, or any solution having an alkaline pH. No drug or chemical agent should be added to NARCAN unless its effect on the chemical and physical stability of the solution has first been established.

General

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Usage in Adults

Opioid Overdose—Known or Suspected: An initial dose of 0.4 mg to 2 mg of NARCAN may be administered intravenously. If the desired degree of counteraction and improvement in respiratory functions are not obtained, it may be repeated at two- to three-minute intervals. If no response is observed after 10 mg of NARCAN have been administered, the diagnosis of opioid-induced or partial opioid-induced toxicity should be questioned. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

Postoperative Opioid Depression: For the partial reversal of opioid depression following the use of opioids during surgery, smaller doses of NARCAN are usually sufficient. The dose of NARCAN should be titrated according to the patient's response. For the initial reversal of respiratory depression, NARCAN should be injected in increments of 0.1 to 0.2 mg intravenously at two- to three-minute intervals to the desired degree of reversal i.e., adequate ventilation and alertness without significant pain or discomfort. Larger than necessary dosage of NARCAN may result in significant reversal of analgesia and increase in blood pressure. Similarly, too rapid reversal may induce nausea, vomiting, sweating or circulatory stress.

Repeat doses of NARCAN may be required within one- to two-hour intervals depending upon the amount, type (i.e., short or long acting) and time interval since last administration of an opioid. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

NARCAN Challenge Test

Used for the diagnosis of suspected opioid tolerance or acute opioid overdosage.

The NARCAN challenge test should not be performed in a patient showing clinical signs or symptoms of opioid withdrawal, or in a patient whose urine contains opioids. The NARCAN challenge test may be administered by either the intravenous or subcutaneous routes.

Intravenous: Inject 0.2 mg NARCAN. Observe for 30 seconds for signs or symptoms of withdrawal. If no evidence of withdrawal, inject 0.6 mg NARCAN. Observe for an additional 20 minutes.

Subcutaneous: Administer 0.8 mg NARCAN. Observe for 20 minutes for signs or symptoms of withdrawal.

Note: Individual patients, especially those with opioid dependence, may respond to lower doses of NARCAN. In some cases, 0.1 mg I.V. NARCAN has produced a diagnostic response.

Interpretation of the Challenge

Monitor vital signs and observe the patient for signs and symptoms of opioid withdrawal. These may include, but are not limited to: nausea, vomiting, dysphoria, yawning, sweating, tearing, rhinorrhea, stuffy nose, craving for opioid, poor appetite, abdominal cramps, sense of fear, skin erythema, disrupted sleep patterns, fidgeting, uneasiness, poor ability to focus, mental lapses, muscle aches or cramps, pupillary dilation, piloerection, fever, changes in blood pressure, pulse or temperature, anxiety, depression, irritability, backache, bone or joint pains, tremors, sensations of skin crawling or fasciculations. If signs or symptoms of withdrawal appear, the test is positive and no additional NARCAN should be administered.

Septic Shock

The optimal dosage of NARCAN or duration of therapy for the treatment of hypotension in septic shock patients has not been established (see **CLINICAL PHARMACOLOGY**).

Usage in Children

Opioid Overdose—Known or Suspected: The usual initial dose in children is 0.01 mg/kg body weight given I.V. If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 0.1 mg/kg body weight may be administered. If an I.V. route of administration is not available, NARCAN may be administered I.M. or S.C. in divided doses. If necessary, NARCAN can be diluted with sterile water for injection.

Postoperative Opioid Depression: Follow the recommendations and cautions under **Adult Postoperative Depres-**

Continued on next page

Narcan—Cont.

sion. For the initial reversal of respiratory depression, NARCAN should be injected in increments of 0.005 mg to 0.01 mg intravenously at two- to three-minute intervals to the desired degree of reversal.

Usage in Neonates

Opioid-induced Depression: The usual initial dose is 0.01 mg/kg body weight administered I.V., I.M. or S.C. This dose may be repeated in accordance with adult administration guidelines for postoperative opioid depression.

HOW SUPPLIED

NARCAN (naloxone hydrochloride injection, USP) for intravenous, intramuscular and subcutaneous administration is available as:

[See table at top of previous page]

Store at 25°C (77°F); excursions permitted to 15°–30°C (59°–86°F). Protect from light.

Store in carton until contents have been used.

Printed in U.S.A. 6487-01/Rev. Jan., 2001

NUBAIN®

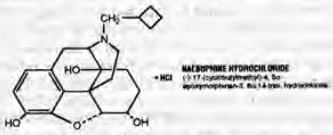
℞

[nū 'bān]

(Nalbuphine Hydrochloride)

DESCRIPTION

NUBAIN (nalbuphine hydrochloride) is a synthetic opioid agonist-antagonist analgesic of the phenanthrene series. It is chemically related to both the widely used opioid antagonist, naloxone, and the potent opioid analgesic, oxymorphone.



NALBUPHINE HYDROCHLORIDE
(-)-17-cyclobutylmethyl-4, 5α-epoxymorphinan-3, 6α, 14-triol, hydrochloride

NUBAIN is a sterile solution suitable for subcutaneous, intramuscular, or intravenous injection. NUBAIN is available in two concentrations, 10 mg and 20 mg of nalbuphine hydrochloride per mL. Both strengths in 10 mL vials contain 0.94% sodium citrate hydrous, 1.26% citric acid anhydrous, and 0.2% of a 9:1 mixture of methylparaben and propylparaben as preservatives; pH is adjusted, if necessary, to 3.5 to 3.7 with hydrochloric acid. The 10 mg/mL strength contains 0.2% sodium chloride.

NUBAIN is also available in ampuls in a sterile, paraben-free formulation in two concentrations, 10 mg and 20 mg of nalbuphine hydrochloride per mL. One mL of each strength contains 0.94% sodium citrate hydrous, and 1.26% citric acid anhydrous; pH is adjusted, if necessary, to 3.5 to 3.7 with hydrochloric acid. The 10 mg/mL strength contains 0.2% sodium chloride.

CLINICAL PHARMACOLOGY

NUBAIN is a potent analgesic. Its analgesic potency is essentially equivalent to that of morphine on a milligram basis. Receptor studies show that NUBAIN binds to mu, kappa, and delta receptors, but not to sigma receptors. NUBAIN is primarily a kappa agonist/partial mu antagonist analgesic.

The onset of action of NUBAIN occurs within 2 to 3 minutes after intravenous administration, and in less than 15 minutes following subcutaneous or intramuscular injection. The plasma half-life of nalbuphine is 5 hours, and in clinical studies the duration of analgesic activity has been reported to range from 3 to 6 hours.

The opioid antagonist activity of NUBAIN is one-fourth as potent as nalorphine and 10 times that of pentazocine.

NUBAIN may produce the same degree of respiratory depression as equianalgesic doses of morphine. However, NUBAIN exhibits a ceiling effect such that increases in dose greater than 30 mg do not produce further respiratory depression.

NUBAIN by itself has potent opioid antagonist activity at doses equal to or lower than its analgesic dose. When administered following or concurrent with mu agonist opioid analgesics (e.g., morphine, oxymorphone, fentanyl), NUBAIN may partially reverse or block opioid-induced respiratory depression from the mu agonist analgesic. NUBAIN may precipitate withdrawal in patients dependent on opioid drugs. NUBAIN should be used with caution in patients who have been receiving mu opioid analgesics on a regular basis.

INDICATIONS AND USAGE

NUBAIN is indicated for the relief of moderate to severe pain. NUBAIN can also be used as a supplement to balanced anesthesia, for preoperative and postoperative analgesia, and for obstetrical analgesia during labor and delivery.

CONTRAINDICATIONS

NUBAIN should not be administered to patients who are hypersensitive to nalbuphine hydrochloride, or to any of the other ingredients in NUBAIN.

WARNINGS

NUBAIN should be administered as a supplement to general anesthesia only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids.

Naloxone, resuscitative and intubation equipment and oxygen should be readily available.

Drug Abuse: Caution should be observed in prescribing NUBAIN for emotionally unstable patients, or for individuals with a history of opioid abuse. Such patients should be closely supervised when long-term therapy is contemplated (see **DRUG ABUSE AND DEPENDENCE**).

Use in Ambulatory Patients: NUBAIN may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Therefore, NUBAIN should be administered with caution to ambulatory patients who should be warned to avoid such hazards.

Use in Emergency Procedures: Maintain patient under observation until recovered from NUBAIN effects that would affect driving or other potentially dangerous tasks.

Use in Pregnancy (other than labor): Safe use of NUBAIN in pregnancy has not been established. Although animal reproductive studies have not revealed teratogenic or embryotoxic effects, nalbuphine should be administered to pregnant women only if clearly needed.

Use During Labor and Delivery: The placental transfer of nalbuphine is high, rapid, and variable with a maternal to fetal ratio ranging from 1:0.37 to 1:1.6. Fetal and neonatal adverse effects that have been reported following the administration of nalbuphine to the mother during labor include fetal bradycardia, respiratory depression at birth, apnea, cyanosis and hypotonia. Maternal administration of naloxone during labor has normalized these effects in some cases. Severe and prolonged fetal bradycardia has been reported. Permanent neurological damage attributed to fetal bradycardia has occurred. A sinusoidal fetal heart rate pattern associated with the use of nalbuphine has also been reported. NUBAIN should be used with caution in women during labor and delivery, and newborns should be monitored for respiratory depression, apnea, bradycardia, and arrhythmias if NUBAIN has been used.

Head Injury and Increased Intracranial Pressure: The possible respiratory depressant effects and the potential of potent analgesics to elevate cerebrospinal fluid pressure (resulting from vasodilation following CO_2 retention) may be markedly exaggerated in the presence of head injury, intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, potent analgesics can produce effects which may obscure the clinical course of patients with head injuries. Therefore, NUBAIN should be used in these circumstances only when essential, and then should be administered with extreme caution.

Interaction With Other Central Nervous System Depressants: Although NUBAIN possesses opioid antagonist activity, there is evidence that in nondependent patients it will not antagonize an opioid analgesic administered just before, concurrently, or just after an injection of NUBAIN. Therefore, patients receiving an opioid analgesic, general anesthetics, phenothiazines, or other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with NUBAIN may exhibit an additive effect. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

PRECAUTIONS

General

Impaired Respiration: At the usual adult dose of 10 mg/70 kg, NUBAIN causes some respiratory depression approximately equal to that produced by equal doses of morphine. However, in contrast to morphine, respiratory depression is not appreciably increased with higher doses of NUBAIN. Respiratory depression induced by NUBAIN can be reversed by NARCAN® (naloxone hydrochloride) when indicated. NUBAIN should be administered with caution at low doses to patients with impaired respiration (e.g., from other medication, uremia, bronchial asthma, severe infection, cyanosis, or respiratory obstructions).

Impaired Renal or Hepatic Function: Because NUBAIN is metabolized in the liver and excreted by the kidneys, NUBAIN should be used with caution in patients with renal or liver dysfunction and administered in reduced amounts.

Myocardial Infarction: As with all potent analgesics, NUBAIN should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Tract Surgery: As with all opioid analgesics, NUBAIN should be used with caution in patients about to undergo surgery of the biliary tract since it may cause spasm of the sphincter of Oddi.

Cardiovascular System: During evaluation of NUBAIN in anesthesia, a higher incidence of bradycardia has been reported in patients who did not receive atropine pre-operatively.

Information for Patients

Patients should be advised of the following information:

— NUBAIN is associated with sedation and may impair mental and physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery.

— NUBAIN is to be used as prescribed by a physician. Dose or frequency should not be increased without first consulting with a physician since NUBAIN may cause psychological or physical dependence.

— The use of NUBAIN with other opioids can cause signs and symptoms of withdrawal.

— Abrupt discontinuation of NUBAIN after prolonged usage may cause signs and symptoms of withdrawal.

Laboratory Tests

NUBAIN may interfere with enzymatic methods for the detection of opioids depending on the specificity/sensitivity of the test. Please consult the test manufacturer for specific details.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenicity was found in a 24-month carcinogenicity study in rats and an 18-month carcinogenicity study in mice at oral doses as high as the equivalent of approximately three times the maximum recommended therapeutic dose.

No evidence of a mutagenic/genotoxic potential to NUBAIN was found in the Ames, Chinese Hamster Ovary HGPRT, and Sister Chromatid Exchange, mouse micronucleus, and rat bone marrow cytogenicity assays. Nalbuphine induced an increased frequency of mutation in mouse lymphoma cells.

Usage in Pregnancy

Teratogenic Effects

Pregnancy Category B—Reproduction studies have been performed in rabbits and in rats at dosages as high as approximately 14 and 31 times respectively the maximum recommended daily dose and revealed no evidence of impaired fertility or harm to the fetus due to NUBAIN. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed (see **WARNINGS**).

Non-teratogenic Effects—Neonatal body weight and survival was reduced when NUBAIN was subcutaneously administered to female rats prior to mating and throughout gestation and lactation or to pregnant rats during the last third of gestation and throughout lactation at doses approximately 8 to 17 times the maximum recommended therapeutic dose. The clinical significance of this effect is unknown.

Use During Labor and Delivery

See **WARNINGS**.

Nursing Mothers

Limited data suggest that NUBAIN (nalbuphine hydrochloride) is excreted in maternal milk but only in a small amount (less than 1% of the administered dose) and with a clinically insignificant effect. Caution should be exercised when NUBAIN is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

ADVERSE REACTIONS

The most frequent adverse reaction in 1066 patients treated in clinical studies with NUBAIN was sedation 381 (36%). Less frequent reactions were: sweaty/clammy 99 (9%), nausea/vomiting 68 (6%), dizziness/vertigo 58 (5%), dry mouth 44 (4%), and headache 27 (3%).

Other adverse reactions which occurred (reported incidence of 1% or less) were:

CNS Effects: Nervousness, depression, restlessness, crying, euphoria, floating, hostility, unusual dreams, confusion, faintness, hallucinations, dysphoria, feeling of heaviness, numbness, tingling, unreality. The incidence of psychotomimetic effects, such as unreality, depersonalization, delusions, dysphoria and hallucinations has been shown to be less than that which occurs with pentazocine.

Cardiovascular: Hypertension, hypotension, bradycardia, tachycardia.

Gastrointestinal: Cramps, dyspepsia, bitter taste.

Respiratory: Depression, dyspnea, asthma.

Dermatologic: Itching, burning, urticaria.

Miscellaneous: Speech difficulty, urinary urgency, blurred vision, flushing and warmth.

Allergic Reactions: Anaphylactic/anaphylactoid and other serious hypersensitivity reactions have been reported following the use of nalbuphine and may require immediate, supportive medical treatment. These reactions may include shock, respiratory distress, respiratory arrest, bradycardia, cardiac arrest, hypotension, or laryngeal edema. Other allergic-type reactions reported include stridor, bronchospasm, wheezing, edema, rash, pruritus, nausea, vomiting, diaphoresis, weakness, and shakiness.

Post-marketing: Other reports include pulmonary edema, agitation and injection site reactions such as pain, swelling, redness, burning, and hot sensations.

DRUG ABUSE AND DEPENDENCE

NUBAIN has been shown to have a low abuse potential. When compared with drugs which are not mixed agonist-antagonists, it has been reported that nalbuphine's potential for abuse would be less than that of codeine and propoxyphene. Drug abuse has been reported infrequently. Psychological and physical dependence and tolerance may follow the abuse or misuse of nalbuphine (see **WARNINGS**).

Care should be taken to avoid increases in dosage or frequency of administration which in susceptible individuals might result in physical dependence.

Abrupt discontinuation of NUBAIN following prolonged use has been followed by symptoms of opioid withdrawal, i.e., abdominal cramps, nausea and vomiting, rhinorrhea, lacrimation, restlessness, anxiety, elevated temperature and piloerection.

Imitrex Injection—Cont.

1. The Purpose of Your Medicine:
IMITREX Injection is intended to relieve your migraine or cluster headache, but not to prevent or reduce the number of attacks you experience. Use IMITREX Injection only to treat an actual migraine or cluster headache attack.

2. Important Questions to Consider Before Taking IMITREX Injection:
If the answer to any of the following questions is **YES** or if you do not know the answer, then please discuss with your doctor before you use IMITREX Injection.

- Are you pregnant? Do you think you might be pregnant? Are you trying to become pregnant? Are you using inadequate contraception? Are you breastfeeding?
- Do you have any chest pain, heart disease, shortness of breath, or irregular heartbeats? Have you had a heart attack?
- Do you have risk factors for heart disease (such as high blood pressure, high cholesterol, obesity, diabetes, smoking, strong family history of heart disease, or you are postmenopausal or a male over 40)?
- Have you had a stroke, transient ischemic attacks (TIAs), or Raynaud syndrome?
- Do you have high blood pressure?
- Have you ever had to stop taking this or any other medication because of an allergy or other problems?
- Are you taking any other migraine medications, including other 5–HT_1 agonists or any other medications containing ergotamine, dihydroergotamine, or methysergide?
- Are you taking any medication for depression (monoamine oxidase inhibitors or selective serotonin reuptake inhibitors [SSRIs])?
- Have you had, or do you have, any disease of the liver or kidney?
- Have you had, or do you have, epilepsy or seizures?
- Is this headache different from your usual migraine attacks?

Remember, if you answered **YES** to any of the above questions, then discuss it with your doctor.

3. The Use of IMITREX Injection During Pregnancy:
Do not use IMITREX Injection if you are pregnant, think you might be pregnant, are trying to become pregnant, or are not using adequate contraception, unless you have discussed this with your doctor.

4. How to Use IMITREX Injection:
Before injecting IMITREX, check with your doctor on acceptable injection sites and see the instructions (on or inside the carton) on discarding empty syringes and loading an autoinjector device.

Never reuse a syringe.

For adults, the usual dose is a single injection given just below the skin. It should be given as soon as the symptoms of your migraine appear, but it may be given at any time during an attack. A second injection may be given if your symptoms of migraine come back. If your symptoms do not improve following the first injection, do not give a second injection for the same attack without first consulting with your doctor. Do not have more than 2 injections in any 24 hours and allow at least 1 hour between each dose.

5. Side Effects to Watch for:

- Some patients experience pain or tightness in the chest or throat when using IMITREX Injection. If this happens to you, then discuss it with your doctor before using any more IMITREX Injection. If the chest pain is severe or does not go away, call your doctor immediately.
- If you have sudden and/or severe abdominal pain following IMITREX Injection, call your doctor immediately.
- Shortness of breath; wheeziness; heart throbbing; swelling of eyelids, face, or lips; or a skin rash, skin lumps, or hives happens rarely. If it happens to you, then tell your doctor immediately. Do not take any more IMITREX Injection unless your doctor tells you to do so.
- Some people may have feelings of tingling, heat, flushing (redness of face lasting a short time), heaviness or pressure after treatment with IMITREX Injection. A few people may feel drowsy, dizzy, tired, or sick. Tell your doctor of these symptoms at your next visit.
- You may experience pain or redness at the site of injection, but this usually lasts less than an hour.
- If you feel unwell in any other way or have any symptoms that you do not understand, you should contact your doctor immediately.

6. What to Do If an Overdose Is Taken:
If you have taken more medication than you have been told, contact either your doctor, hospital emergency department, or nearest poison control center immediately.

7. Storing Your Medicine:
Keep your medicine in a safe place where children cannot reach it. It may be harmful to children.
Store your medication away from heat and light. Keep your medication in the case provided and do not store at temperatures above 86°F (30°C).
If your medication has expired (the expiration date is printed on the treatment pack), throw it away as instructed. Do not throw away your autoinjector.
If your doctor decides to stop your treatment, do not keep any leftover medicine unless your doctor tells you to. Throw away your medicine as instructed.

GlaxoSmithKline, Research Triangle Park, NC 27709

March 2001/RL-915

Shown in Product Identification Guide, page 316

IMITREX® Ⓡ

[im' I-trĕx"]
(sumatriptan)
Nasal Spray

DESCRIPTION

IMITREX (sumatriptan) Nasal Spray contains sumatriptan, a selective 5-hydroxytryptamine$_1$ receptor subtype agonist. Sumatriptan is chemically designated as 3-[2-(dimethylamino) ethyl] -N-methyl-1H-indole-5-methanesulfonamide.

The empirical formula is $C_{14}H_{21}N_3O_2S$, representing a molecular weight of 295.4. Sumatriptan is a white to off-white powder that is readily soluble in water and in saline. Each IMITREX Nasal Spray contains 5 or 20 mg of sumatriptan in a 100-µL unit dose aqueous buffered solution containing monobasic potassium phosphate NF, anhydrous dibasic sodium phosphate USP, sulfuric acid NF, sodium hydroxide NF, and purified water USP. The pH of the solution is approximately 5.5. The osmolality of the solution is 372 or 742 mOsmol for the 5- and 20-mg IMITREX Nasal Spray, respectively.

CLINICAL PHARMACOLOGY

Mechanism of Action: Sumatriptan is an agonist for a vascular 5-hydroxytryptamine$_1$ receptor subtype (probably a member of the 5-HT_{1D} family) having only a weak affinity for 5-HT_{1A}, 5-HT_{5A}, and 5-HT_7 receptors and no significant affinity (as measured using standard radioligand binding assays) or pharmacological activity at 5-HT_2, 5-HT_3, or 5-HT_4 receptor subtypes or at alpha$_1$-, alpha$_2$-, or beta-adrenergic; dopamine$_1$; dopamine$_2$; muscarinic; or benzodiazepine receptors.

The vascular 5-HT_1 receptor subtype that sumatriptan activates is present on cranial arteries in both dog and primate, on the human basilar artery, and in the vasculature of human dura mater and mediates vasoconstriction. This action in humans correlates with the relief of migraine headache. In addition to causing vasoconstriction, experimental data from animal studies show that sumatriptan also activates 5-HT_1 receptors on peripheral terminals of the trigeminal nerve innervating cranial blood vessels. Such an action may contribute to the antimigrainous effect of sumatriptan in humans.

In the anesthetized dog, sumatriptan selectively reduces the carotid arterial blood flow with little or no effect on arterial blood pressure or total peripheral resistance. In the cat, sumatriptan selectively constricts the carotid arteriovenous anastomoses while having little effect on blood flow or resistance in cerebral or extracerebral tissues.

Pharmacokinetics: In a study of 20 female volunteers, the mean maximum concentration following a 5- and 20-mg intranasal dose was 5 and 16 ng/mL, respectively. The mean C_{max} following a 6-mg subcutaneous injection is 71 ng/mL (range, 49 to 110 ng/mL). The mean C_{max} is 18 ng/mL (range, 7 to 47 ng/mL) following oral dosing with 25 mg and 51 ng/mL (range, 28 to 100 ng/mL) following oral dosing with 100 mg of sumatriptan. In a study of 24 male volunteers, the bioavailability relative to subcutaneous injection was low, approximately 17%, primarily due to presystemic metabolism and partly due to incomplete absorption.

Protein binding, determined by equilibrium dialysis over the concentration range of 10 to 1,000 ng/mL, is low, approximately 14% to 21%. The effect of sumatriptan on the protein binding of other drugs has not been evaluated, but would be expected to be minor, given the low rate of protein binding. The mean volume of distribution after subcutaneous dosing is 2.7 L/kg and the total plasma clearance is approximately 1,200 mL/min.

The elimination half-life of sumatriptan administered as a nasal spray is approximately 2 hours, similar to the half-life seen after subcutaneous injection. Only 3% of the dose is excreted in the urine as unchanged sumatriptan; 42% of the dose is excreted as the major metabolite, the indole acetic acid analogue of sumatriptan.

Clinical and pharmacokinetic data indicate that administration of two 5-mg doses, 1 dose in each nostril, is equivalent to administration of a single 10-mg dose in 1 nostril.

Special Populations: ***Renal Impairment:*** The effect of renal impairment on the pharmacokinetics of sumatriptan has not been examined, but little clinical effect would be expected as sumatriptan is largely metabolized to an inactive substance.

Hepatic Impairment: The effect of hepatic disease on the pharmacokinetics of subcutaneously and orally administered sumatriptan has been evaluated, but the intranasal dosage form has not been studied in hepatic impairment. There were no statistically significant differences in the pharmacokinetics of subcutaneously administered sumatriptan in hepatically impaired patients compared to healthy controls. However, the liver plays an important role in the presystemic clearance of orally administered sumatriptan. In 1 small study involving oral sumatriptan in hepatically impaired patients (n = 8) matched for sex, age, and weight with healthy subjects, the hepatically impaired patients had an approximately 70% increase in AUC and C_{max} and a T_{max} 40 minutes earlier compared to the healthy subjects. The bioavailability of nasally absorbed sumatriptan following intranasal administration, which would not undergo first-pass metabolism, should not be altered in hepatically impaired patients. The bioavailability of the swallowed portion of the intranasal sumatriptan dose has not been determined, but would be increased in these patients. The swallowed intranasal dose is small, however, compared to the usual oral dose, so that its impact should be minimal.

Age: The pharmacokinetics of oral sumatriptan in the elderly (mean age, 72 years, 2 males and 4 females) and in patients with migraine (mean age, 38 years, 25 males and 155 females) were similar to that in healthy male subjects (mean age, 30 years). Intranasal sumatriptan has not been evaluated for age differences (see PRECAUTIONS: Geriatric Use).

Race: The systemic clearance and C_{max} of sumatriptan were similar in black (n = 34) and Caucasian (n = 38) healthy male subjects. Intranasal sumatriptan has not been evaluated for race differences.

Drug Interactions: ***Monoamine Oxidase Inhibitors:*** Treatment with monoamine oxidase inhibitors generally leads to an increase of sumatriptan plasma levels (see CONTRAINDICATIONS and PRECAUTIONS).

MAOI interaction studies have not been performed with intranasal sumatriptan. Due to gut and hepatic metabolic first-pass effects, the increase of systemic exposure after coadministration of an MAO-A inhibitor with oral sumatriptan is greater than after coadministration of the MAOI with subcutaneous sumatriptan. The effects of an MAOI on systemic exposure after intranasal sumatriptan would be expected to be greater than the effect after subcutaneous sumatriptan but smaller than the effect after oral sumatriptan because only swallowed drug would be subject to first-pass effects.

In a study of 14 healthy females, pretreatment with an MAO-A inhibitor decreased the clearance of subcutaneous sumatriptan. Under the conditions of this experiment, the result was a 2-fold increase in the area under the sumatriptan plasma concentration x time curve (AUC), corresponding to a 40% increase in elimination half-life. This interaction was not evident with an MAO-B inhibitor.

A small study evaluating the effect of pretreatment with an MAO-A inhibitor on the bioavailability from a 25-mg oral sumatriptan tablet resulted in an approximately 7-fold increase in systemic exposure.

Xylometazoline: An in vivo drug interaction study indicated that 3 drops of xylometazoline (0.1% w/v), a decongestant, administered 15 minutes prior to a 20-mg nasal dose of sumatriptan did not alter the pharmacokinetics of sumatriptan.

CLINICAL TRIALS

The efficacy of IMITREX Nasal Spray in the acute treatment of migraine headaches was demonstrated in 8, randomized, double-blind, placebo-controlled studies, of which 5 used the recommended dosing regimen and used the marketed formulation. Patients enrolled in these 5 studies were predominately female (86%) and Caucasian (95%), with a mean age of 41 (range of 18 to 65). Patients were instructed to treat a moderate to severe headache. Headache response, defined as a reduction in headache severity from moderate or severe pain to mild or no pain, was assessed up to 2 hours after dosing. Associated symptoms such as nausea, photophobia, and phonophobia were also assessed. Maintenance of response was assessed for up to 24 hours postdose. A second dose of IMITREX Nasal Spray or other medication was allowed 2 to 24 hours after the initial treatment for recurrent headache. The frequency and time to use of these additional treatments were also determined. In all studies, doses of 10 and 20 mg were compared to placebo in the treatment of 1 to 3 migraine attacks. Patients received doses as a single spray into 1 nostril. In 2 studies, a 5-mg dose was also evaluated.

In all 5 trials utilizing the market formulation and recommended dosage regimen, the percentage of patients achieving headache response 2 hours after treatment was significantly greater among patients receiving IMITREX Nasal Spray at all doses (with one exception) compared to those who received placebo. In 4 of the 5 studies, there was a statistically significant greater percentage of patients with headache response at 2 hours in the 20-mg group when compared to the lower dose groups (5 and 10 mg). There were no statistically significant differences between the 5- and 10-mg dose groups in any study. The results from the 5 controlled clinical trials are summarized in Table 1. Note that, in general, comparisons of results obtained in studies conducted under different conditions by different investigators with different samples of patients are ordinarily unreliable for purposes of quantitative comparison.

[See table 1 at bottom of next page]

The estimated probability of achieving an initial headache response over the 2 hours following treatment is depicted in Figure 1.

[See figure 1 at top of next column]

For patients with migraine-associated nausea, photophobia, and phonophobia at baseline, there was a lower incidence of these symptoms at 2 hours following administration of IMITREX Nasal Spray compared to placebo.

Two to 24 hours following the initial dose of study treatment, patients were allowed to use additional treatment for pain relief in the form of a second dose of study treatment or other medication. The estimated probability of patients taking a second dose or other medication for migraine over the 24 hours following the initial dose of study treatment is summarized in Figure 2.

[See figure 2 at top of next column]

Imitrex Injection—Cont.

1. The Purpose of Your Medicine:
IMITREX Injection is intended to relieve your migraine or cluster headache, but not to prevent or reduce the number of attacks you experience. Use IMITREX Injection only to treat an actual migraine or cluster headache attack.

2. Important Questions to Consider Before Taking IMITREX Injection:
If the answer to any of the following questions is **YES** or if you do not know the answer, then please discuss with your doctor before you use IMITREX Injection.

- Are you pregnant? Do you think you might be pregnant? Are you trying to become pregnant? Are you using inadequate contraception? Are you breastfeeding?
- Do you have any chest pain, heart disease, shortness of breath, or irregular heartbeats? Have you had a heart attack?
- Do you have risk factors for heart disease (such as high blood pressure, high cholesterol, obesity, diabetes, smoking, strong family history of heart disease, or you are postmenopausal or a male over 40)?
- Have you had a stroke, transient ischemic attacks (TIAs), or Raynaud syndrome?
- Do you have high blood pressure?
- Have you ever had to stop taking this or any other medication because of an allergy or other problems?
- Are you taking any other migraine medications, including other 5–HT_1 agonists or any other medications containing ergotamine, dihydroergotamine, or methysergide?
- Are you taking any medication for depression (monoamine oxidase inhibitors or selective serotonin reuptake inhibitors [SSRIs])?
- Have you had, or do you have, any disease of the liver or kidney?
- Have you had, or do you have, epilepsy or seizures?
- Is this headache different from your usual migraine attacks?

Remember, if you answered **YES** to any of the above questions, then discuss it with your doctor.

3. The Use of IMITREX Injection During Pregnancy:
Do not use IMITREX Injection if you are pregnant, think you might be pregnant, are trying to become pregnant, or are not using adequate contraception, unless you have discussed this with your doctor.

4. How to Use IMITREX Injection:
Before injecting IMITREX, check with your doctor on acceptable injection sites and see the instructions (on or inside the carton) on discarding empty syringes and loading an autoinjector device.

Never reuse a syringe.

For adults, the usual dose is a single injection given just below the skin. It should be given as soon as the symptoms of your migraine appear, but it may be given at any time during an attack. A second injection may be given if your symptoms of migraine come back. If your symptoms do not improve following the first injection, do not give a second injection for the same attack without first consulting with your doctor. Do not have more than 2 injections in any 24 hours and allow at least 1 hour between each dose.

5. Side Effects to Watch for:

- Some patients experience pain or tightness in the chest or throat when using IMITREX Injection. If this happens to you, then discuss it with your doctor before using any more IMITREX Injection. If the chest pain is severe or does not go away, call your doctor immediately.
- If you have sudden and/or severe abdominal pain following IMITREX Injection, call your doctor immediately.
- Shortness of breath; wheeziness; heart throbbing; swelling of eyelids, face, or lips; or a skin rash, skin lumps, or hives happens rarely. If it happens to you, then tell your doctor immediately. Do not take any more IMITREX Injection unless your doctor tells you to do so.
- Some people may have feelings of tingling, heat, flushing (redness of face lasting a short time), heaviness or pressure after treatment with IMITREX Injection. A few people may feel drowsy, dizzy, tired, or sick. Tell your doctor of these symptoms at your next visit.
- You may experience pain or redness at the site of injection, but this usually lasts less than an hour.
- If you feel unwell in any other way or have any symptoms that you do not understand, you should contact your doctor immediately.

6. What to Do If an Overdose Is Taken:
If you have taken more medication than you have been told, contact either your doctor, hospital emergency department, or nearest poison control center immediately.

7. Storing Your Medicine:
Keep your medicine in a safe place where children cannot reach it. It may be harmful to children.
Store your medication away from heat and light. Keep your medication in the case provided and do not store at temperatures above 86°F (30°C).
If your medication has expired (the expiration date is printed on the treatment pack), throw it away as instructed. Do not throw away your autoinjector.
If your doctor decides to stop your treatment, do not keep any leftover medicine unless your doctor tells you to. Throw away your medicine as instructed.

GlaxoSmithKline, Research Triangle Park, NC 27709

March 2001/RL-915

Shown in Product Identification Guide, page 316

IMITREX® Rx

[Im' I-trĕx"]
(sumatriptan)
Nasal Spray

DESCRIPTION

IMITREX (sumatriptan) Nasal Spray contains sumatriptan, a selective 5-hydroxytryptamine$_1$ receptor subtype agonist. Sumatriptan is chemically designated as 3-[2-(dimethylamino) ethyl] -N-methyl-1H-indole-5-methanesulfonamide.

The empirical formula is $C_{14}H_{21}N_3O_2S$, representing a molecular weight of 295.4. Sumatriptan is a white to off-white powder that is readily soluble in water and in saline. Each IMITREX Nasal Spray contains 5 or 20 mg of sumatriptan in a 100-µL unit dose aqueous buffered solution containing monobasic potassium phosphate NF, anhydrous dibasic sodium phosphate USP, sulfuric acid NF, sodium hydroxide NF, and purified water USP. The pH of the solution is approximately 5.5. The osmolality of the solution is 372 or 742 mOsmol for the 5- and 20-mg IMITREX Nasal Spray, respectively.

CLINICAL PHARMACOLOGY

Mechanism of Action: Sumatriptan is an agonist for a vascular 5-hydroxytryptamine$_1$ receptor subtype (probably a member of the 5-HT_{1D} family) having only a weak affinity for 5-HT_{1A}, 5-HT_{5A}, and 5-HT_7 receptors and no significant affinity (as measured using standard radioligand binding assays) or pharmacological activity at 5-HT_2, 5-HT_3, or 5-HT_4 receptor subtypes or at alpha$_1$-, alpha$_2$-, or beta-adrenergic; dopamine$_1$; dopamine$_2$; muscarinic; or benzodiazepine receptors.

The vascular 5-HT_1 receptor subtype that sumatriptan activates is present on cranial arteries in both dog and primate, on the human basilar artery, and in the vasculature of human dura mater and mediates vasoconstriction. This action in humans correlates with the relief of migraine headache. In addition to causing vasoconstriction, experimental data from animal studies show that sumatriptan also activates 5-HT_1 receptors on peripheral terminals of the trigeminal nerve innervating cranial blood vessels. Such an action may contribute to the antimigrainous effect of sumatriptan in humans.

In the anesthetized dog, sumatriptan selectively reduces the carotid arterial blood flow with little or no effect on arterial blood pressure or total peripheral resistance. In the cat, sumatriptan selectively constricts the carotid arteriovenous anastomoses while having little effect on blood flow or resistance in cerebral or extracerebral tissues.

Pharmacokinetics: In a study of 20 female volunteers, the mean maximum concentration following a 5- and 20-mg intranasal dose was 5 and 16 ng/mL, respectively. The mean C_{max} following a 6-mg subcutaneous injection is 71 ng/mL (range, 49 to 110 ng/mL). The mean C_{max} is 18 ng/mL (range, 7 to 47 ng/mL) following oral dosing with 25 mg and 51 ng/mL (range, 28 to 100 ng/mL) following oral dosing with 100 mg of sumatriptan. In a study of 24 male volunteers, the bioavailability relative to subcutaneous injection was low, approximately 17%, primarily due to presystemic metabolism and partly due to incomplete absorption.

Protein binding, determined by equilibrium dialysis over the concentration range of 10 to 1,000 ng/mL, is low, approximately 14% to 21%. The effect of sumatriptan on the protein binding of other drugs has not been evaluated, but would be expected to be minor, given the low rate of protein binding. The mean volume of distribution after subcutaneous dosing is 2.7 L/kg and the total plasma clearance is approximately 1,200 mL/min.

The elimination half-life of sumatriptan administered as a nasal spray is approximately 2 hours, similar to the half-life seen after subcutaneous injection. Only 3% of the dose is excreted in the urine as unchanged sumatriptan; 42% of the dose is excreted as the major metabolite, the indole acetic acid analogue of sumatriptan.

Clinical and pharmacokinetic data indicate that administration of two 5-mg doses, 1 dose in each nostril, is equivalent to administration of a single 10-mg dose in 1 nostril.

Special Populations: ***Renal Impairment:*** The effect of renal impairment on the pharmacokinetics of sumatriptan has not been examined, but little clinical effect would be expected as sumatriptan is largely metabolized to an inactive substance.

Hepatic Impairment: The effect of hepatic disease on the pharmacokinetics of subcutaneously and orally administered sumatriptan has been evaluated, but the intranasal dosage form has not been studied in hepatic impairment. There were no statistically significant differences in the pharmacokinetics of subcutaneously administered sumatriptan in hepatically impaired patients compared to healthy controls. However, the liver plays an important role in the presystemic clearance of orally administered sumatriptan. In 1 small study involving oral sumatriptan in hepatically impaired patients (n = 8) matched for sex, age, and weight with healthy subjects, the hepatically impaired patients had an approximately 70% increase in AUC and C_{max} and a T_{max} 40 minutes earlier compared to the healthy subjects. The bioavailability of nasally absorbed sumatriptan following intranasal administration, which would not undergo first-pass metabolism, should not be altered in hepatically impaired patients. The bioavailability of the swallowed portion of the intranasal sumatriptan dose has not been determined, but would be increased in these patients. The swallowed intranasal dose is small, however, compared to the usual oral dose, so that its impact should be minimal.

Age: The pharmacokinetics of oral sumatriptan in the elderly (mean age, 72 years, 2 males and 4 females) and in patients with migraine (mean age, 38 years, 25 males and 155 females) were similar to that in healthy male subjects (mean age, 30 years). Intranasal sumatriptan has not been evaluated for age differences (see PRECAUTIONS: Geriatric Use).

Race: The systemic clearance and C_{max} of sumatriptan were similar in black (n = 34) and Caucasian (n = 38) healthy male subjects. Intranasal sumatriptan has not been evaluated for race differences.

Drug Interactions: ***Monoamine Oxidase Inhibitors:*** Treatment with monoamine oxidase inhibitors generally leads to an increase of sumatriptan plasma levels (see CONTRAINDICATIONS and PRECAUTIONS).

MAOI interaction studies have not been performed with intranasal sumatriptan. Due to gut and hepatic metabolic first-pass effects, the increase of systemic exposure after coadministration of an MAO-A inhibitor with oral sumatriptan is greater than after coadministration of the MAOI with subcutaneous sumatriptan. The effects of an MAOI on systemic exposure after intranasal sumatriptan would be expected to be greater than the effect after subcutaneous sumatriptan but smaller than the effect after oral sumatriptan because only swallowed drug would be subject to first-pass effects.

In a study of 14 healthy females, pretreatment with an MAO-A inhibitor decreased the clearance of subcutaneous sumatriptan. Under the conditions of this experiment, the result was a 2-fold increase in the area under the sumatriptan plasma concentration x time curve (AUC), corresponding to a 40% increase in elimination half-life. This interaction was not evident with an MAO-B inhibitor.

A small study evaluating the effect of pretreatment with an MAO-A inhibitor on the bioavailability from a 25-mg oral sumatriptan tablet resulted in an approximately 7-fold increase in systemic exposure.

Xylometazoline: An in vivo drug interaction study indicated that 3 drops of xylometazoline (0.1% w/v), a decongestant, administered 15 minutes prior to a 20-mg nasal dose of sumatriptan did not alter the pharmacokinetics of sumatriptan.

CLINICAL TRIALS

The efficacy of IMITREX Nasal Spray in the acute treatment of migraine headaches was demonstrated in 8, randomized, double-blind, placebo-controlled studies, of which 5 used the recommended dosing regimen and used the marketed formulation. Patients enrolled in these 5 studies were predominately female (86%) and Caucasian (95%), with a mean age of 41 (range of 18 to 65). Patients were instructed to treat a moderate to severe headache. Headache response, defined as a reduction in headache severity from moderate or severe pain to mild or no pain, was assessed up to 2 hours after dosing. Associated symptoms such as nausea, photophobia, and phonophobia were also assessed. Maintenance of response was assessed for up to 24 hours postdose. A second dose of IMITREX Nasal Spray or other medication was allowed 2 to 24 hours after the initial treatment for recurrent headache. The frequency and time to use of these additional treatments were also determined. In all studies, doses of 10 and 20 mg were compared to placebo in the treatment of 1 to 3 migraine attacks. Patients received doses as a single spray into 1 nostril. In 2 studies, a 5-mg dose was also evaluated.

In all 5 trials utilizing the market formulation and recommended dosage regimen, the percentage of patients achieving headache response 2 hours after treatment was significantly greater among patients receiving IMITREX Nasal Spray at all doses (with one exception) compared to those who received placebo. In 4 of the 5 studies, there was a statistically significant greater percentage of patients with headache response at 2 hours in the 20-mg group when compared to the lower dose groups (5 and 10 mg). There were no statistically significant differences between the 5- and 10-mg dose groups in any study. The results from the 5 controlled clinical trials are summarized in Table 1. Note that, in general, comparisons of results obtained in studies conducted under different conditions by different investigators with different samples of patients are ordinarily unreliable for purposes of quantitative comparison.

[See table 1 at bottom of next page]

The estimated probability of achieving an initial headache response over the 2 hours following treatment is depicted in Figure 1.

[See figure 1 at top of next column]

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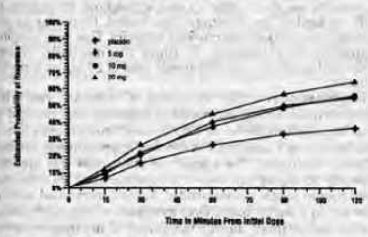
Two to 24 hours following the initial dose of study treatment, patients were allowed to use additional treatment for pain relief in the form of a second dose of study treatment or other medication. The estimated probability of patients taking a second dose or other medication for migraine over the 24 hours following the initial dose of study treatment is summarized in Figure 2.

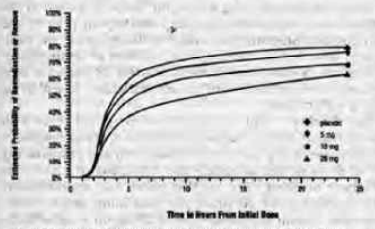
[See figure 2 at top of next column]

Figure 1. Estimated Probability of Achieving Initial Headache Response Within 120 Minutes*



*The figure shows the probability over time of obtaining headache response (no or mild pain) following treatment with intranasal sumatriptan. The averages displayed are based on pooled data from the 5 clinical controlled trials providing evidence of efficacy. Kaplan-Meier plot with patients not achieving response within 120 minutes censored to 120 minutes

Figure 2. The Estimated Probability of Patients Taking a Second Dose or Other Medication for Migraine Over the 24 Hours Following the Initial Dose of Study Treatment*



*Kaplan-Meier plot based on data obtained in the 3 clinical controlled trials providing evidence of efficacy with patients not using additional treatments censored to 24 hours. Plot also includes patients who had no response to the initial dose. No remedication was allowed within 2 hours postdose.

There is evidence that doses above 20 mg do not provide a greater effect than 20 mg. There was no evidence to suggest that treatment with sumatriptan was associated with an increase in the severity of recurrent headaches. The efficacy of IMITREX Nasal Spray was unaffected by presence of aura; duration of headache prior to treatment; gender, age, or weight of the patient; or concomitant use of common migraine prophylactic drugs (e.g., beta-blockers, calcium channel blockers, tricyclic antidepressants). There were insufficient data to assess the impact of race on efficacy.

INDICATIONS AND USAGE

IMITREX Nasal Spray is indicated for the acute treatment of migraine attacks with or without aura in adults.

IMITREX Nasal Spray is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine (see CONTRAINDICATIONS). Safety and effectiveness of IMITREX Nasal Spray have not been established for cluster headache, which is present in an older, predominantly male population.

CONTRAINDICATIONS

IMITREX Nasal Spray should not be given to patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes. In addition, patients with other significant underlying cardiovascular diseases should not receive IMITREX Nasal Spray. Ischemic cardiac syndromes include, but are not limited to, angina pectoris of any type (e.g., stable angina of effort and vasospastic forms of angina such as the Prinzmetal variant), all forms of myocardial infarction, and silent myocardial ischemia. Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as transient ischemic attacks. Peripheral vascular disease includes, but is not limited to, ischemic bowel disease (see WARNINGS).

Because IMITREX Nasal Spray may increase blood pressure, it should not be given to patients with uncontrolled hypertension.

Concurrent administration of MAO-A inhibitors or use within 2 weeks of discontinuation of MAO-A inhibitor therapy is contraindicated (see CLINICAL PHARMACOLOGY: Drug Interactions and PRECAUTIONS: Drug Interactions).

IMITREX Nasal Spray and any ergotamine-containing or ergot-type medication (like dihydroergotamine or methysergide) should not be used within 24 hours of each other, nor should IMITREX Nasal Spray and another 5-HT_1 agonist.

IMITREX Nasal Spray should not be administered to patients with hemiplegic or basilar migraine.

IMITREX Nasal Spray is contraindicated in patients with hypersensitivity to sumatriptan or any of its components.

IMITREX Nasal Spray is contraindicated in patients with severe hepatic impairment.

WARNINGS

IMITREX Nasal Spray should only be used where a clear diagnosis of migraine headache has been established.

Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events: Sumatriptan should not be given to patients with documented ischemic or vasospastic coronary artery disease (CAD) (see CONTRAINDICATIONS). It is strongly recommended that sumatriptan not be given to patients in whom unrecognized CAD is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history or electrocardiographic investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, sumatriptan should not be administered (see CONTRAINDICATIONS).

For patients with risk factors predictive of CAD, who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of sumatriptan nasal spray take place in the setting of a physician's office or similar medically staffed and equipped facility unless the patient has previously received sumatriptan. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining on the first occasion of use an electrocardiogram (ECG) during the interval immediately following IMITREX Nasal Spray, in these patients with risk factors.

It is recommended that patients who are intermittent long-term users of sumatriptan and who have or acquire risk factors predictive of CAD, as described above, undergo periodic interval cardiovascular evaluation as they continue to use sumatriptan.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to sumatriptan.

Drug-Associated Cardiac Events and Fatalities: Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of IMITREX® (sumatriptan succinate) Injection or IMITREX® (sumatriptan succinate) Tablets. Considering the extent of use of sumatriptan in patients with migraine, the incidence of these events is extremely low. The fact that sumatriptan can cause coronary vasospasm, that some of these events have occurred in patients with no prior cardiac disease history and with documented absence of CAD, and the close proximity of the events to sumatriptan use support the conclusion that some of these cases were caused by the drug. In many cases, however, where there has been known underlying coronary artery disease, the relationship is uncertain.

Premarketing Experience With Sumatriptan: Among approximately 4,000 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of sumatriptan nasal spray, 1 patient experienced an asymptomatic subendocardial infarction possibly subsequent to a coronary vasospastic event.

Of 6,348 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of oral sumatriptan, 2 experienced clinical adverse events shortly after receiving oral sumatriptan that may have reflected coronary vasospasm. Neither of these adverse events was associated with a serious clinical outcome.

Among the more than 1,900 patients with migraine who participated in premarketing controlled clinical trials of subcutaneous sumatriptan, there were 8 patients who sustained clinical events during or shortly after receiving sumatriptan that may have reflected coronary artery vasospasm. Six of these 8 patients had ECG changes consistent with transient ischemia, but without accompanying clinical symptoms or signs. Of these 8 patients, 4 had either findings suggestive of CAD or risk factors predictive of CAD prior to study enrollment.

Postmarketing Experience With Sumatriptan: Serious cardiovascular events, some resulting in death, have been reported in association with the use of IMITREX Injection or IMITREX Tablets. The uncontrolled nature of postmarketing surveillance, however, makes it impossible to determine definitively the proportion of the reported cases that were actually caused by sumatriptan or to reliably assess causation in individual cases. On clinical grounds, the longer the latency between the administration of IMITREX and the onset of the clinical event, the less likely the association is to be causative. Accordingly, interest has focused on events beginning within 1 hour of the administration of IMITREX.

Cardiac events that have been observed to have onset within 1 hour of sumatriptan administration include: coronary artery vasospasm, transient ischemia, myocardial infarction, ventricular tachycardia and ventricular fibrillation, cardiac arrest, and death.

Some of these events occurred in patients who had no findings of CAD and appear to represent consequences of coronary artery vasospasm. However, among domestic reports of serious cardiac events within 1 hour of sumatriptan administration, almost all of the patients had risk factors predictive of CAD and the presence of significant underlying CAD was established in most cases (see CONTRAINDICATIONS).

Drug-Associated Cerebrovascular Events and Fatalities: Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with oral or subcutaneous sumatriptan, and some have resulted in fatalities. The relationship of sumatriptan to these events is uncertain. In a number of cases, it appears possible that the cerebrovascular events were primary, sumatriptan having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine when they were not. As with other acute migraine therapies, before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions. It should also be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., cerebrovascular accident, transient ischemic attack).

Other Vasospasm-Related Events: Sumatriptan may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported.

Increase in Blood Pressure: Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients with and without a history of hypertension. Sumatriptan is contraindicated in patients with uncontrolled hypertension (see CONTRAINDICATIONS). Sumatriptan should be administered with caution to patients with controlled hypertension as transient increases in blood pressure and peripheral vascular resistance have been observed in a small proportion of patients.

Local Irritation: Of the 3,378 patients using the nasal spray (5-, 10-, or 20-mg doses) on 1 or 2 occasions in controlled clinical studies, approximately 5% noted irritation in the nose and throat. Irritative symptoms such as burning, numbness, paresthesia, discharge, pain or soreness were noted to be severe in about 1% of patients treated. The

Continued on next page

Table 1. Percentage of Patients With Headache Response (No or Mild Pain) 2 Hours Following Treatment

	Placebo	IMITREX Nasal Spray 5 mg	IMITREX Nasal Spray 10 mg	IMITREX Nasal Spray 20 mg
Study 1	25% (n = 63)	49%* (n = 121)	46%* (n = 112)	64%*†‡ (n = 118)
Study 2	25% (n = 138)	Not applicable	44%* (n = 273)	55%*† (n = 277)
Study 3	35% (n = 100)	Not applicable	54%* (n = 106)	63%* (n = 202)
Study 4	29% (n = 112)	Not applicable	43% (n = 106)	62%*† (n = 215)
Study 5§	36% (n = 198)	45%* (n = 296)	53%* (n = 291)	60%*‡ (n = 286)

*$p \leq 0.05$ in comparison with placebo.
†$p < 0.05$ in comparison with 10 mg.
‡$p < 0.05$ in comparison with 5 mg.
§Data are for attack 1 only of multiattack study for comparison.

This product information is based on labeling in effect on August 1, 2002. Further information is available at: GlaxoSmithKline, PO Box 13398, Research Triangle Park, NC 27709. 1-888-825-5249. Corporate Web Site: www.gsk.com

Imitrex Nasal Spray—Cont.

symptoms were transient and in approximately 60% of the cases, the symptoms resolved in less than 2 hours. Limited examinations of the nose and throat did not reveal any clinically noticeable injury in these patients. The consequences of extended and repeated use of IMITREX Nasal Spray on the nasal and/or respiratory mucosa have not been systematically evaluated in patients.

No increase in the incidence of local irritation was observed in patients using IMITREX Nasal Spray repeatedly for up to 1 year.

In inhalation studies in rats dosed daily for up to 1 month at exposures as low as one half the maximum daily human exposure (based on dose per surface area of nasal cavity), epithelial hyperplasia (with and without keratinization) and squamous metaplasia were observed in the larynx at all doses tested. These changes were partially reversible after a 2-week drug-free period. When dogs were dosed daily with various formulations by intranasal instillation for up to 13 weeks at exposures of 2 to 4 times the maximum daily human exposure (based on dose per surface area of nasal cavity), respiratory and nasal mucosa exhibited evidence of epithelial hyperplasia, focal squamous metaplasia, granulomata, bronchitis, and fibrosing alveolitis. A no-effect dose was not established. The changes observed in both species are not considered to be signs of either preneoplastic or neoplastic transformation.

Local effects on nasal and respiratory tissues after chronic intranasal dosing in animals have not been studied.

Concomitant Drug Use: In patients taking MAO-A inhibitors, sumatriptan plasma levels attained after treatment with recommended doses are 2-fold (following subcutaneous administration) to 7-fold (following oral administration) higher than those obtained under other conditions. Accordingly, the coadministration of IMITREX Nasal Spray and an MAO-A inhibitor is contraindicated (see CLINICAL PHARMACOLOGY and CONTRAINDICATIONS).

Hypersensitivity: Hypersensitivity (anaphylaxis/anaphylactoid) reactions have occurred on rare occasions in patients receiving sumatriptan. Such reactions can be life threatening or fatal. In general, hypersensitivity reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens (see CONTRAINDICATIONS).

PRECAUTIONS

General: Chest discomfort and jaw or neck tightness have been reported infrequently following the administration of IMITREX Nasal Spray and have also been reported following use of IMITREX Tablets. Chest, jaw, or neck tightness is relatively common after administration of IMITREX Injection. Only rarely have these symptoms been associated with ischemic ECG changes. However, because sumatriptan may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following sumatriptan should be evaluated for the presence of CAD or a predisposition to Prinzmetal variant angina before receiving additional doses of sumatriptan, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud syndrome following sumatriptan should be evaluated for atherosclerosis or predisposition to vasospasm (see WARNINGS).

IMITREX Nasal Spray should also be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs, such as impaired hepatic or renal function.

There have been rare reports of seizure following administration of sumatriptan. Sumatriptan should be used with caution in patients with a history of epilepsy or structural brain lesions that lower their seizure threshold.

Care should be taken to exclude other potentially serious neurologic conditions before treating headache in patients not previously diagnosed with migraine headache or who experience a headache that is atypical for them. There have been rare reports where patients received sumatriptan for severe headaches that were subsequently shown to have been secondary to an evolving neurologic lesion (see WARNINGS).

For a given attack, if a patient does not respond to the first dose of sumatriptan, the diagnosis of migraine headache should be reconsidered before administration of a second dose

Binding to Melanin-Containing Tissues: In rats treated with a single subcutaneous dose (0.5 mg/kg) or oral dose (2 mg/kg) of radiolabeled sumatriptan, the elimination half-life of radioactivity from the eye was 15 and 23 days, respectively, suggesting that sumatriptan and/or its metabolites bind to the melanin of the eye. Comparable studies were not performed by the intranasal route. Because there could be an accumulation in melanin-rich tissues over time, this raises the possibility that sumatriptan could cause toxicity in these tissues after extended use. However, no effects on the retina related to treatment with sumatriptan were noted in any of the oral or subcutaneous toxicity studies. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic effects.

Corneal Opacities: Sumatriptan causes corneal opacities and defects in the corneal epithelium in dogs; this raises the possibility that these changes may occur in humans. While patients were not systematically evaluated for these changes in clinical trials, and no specific recommendations for monitoring are being offered, prescribers should be aware of the possibility of these changes (see ANIMAL TOXICOLOGY).

Information for Patients: See PATIENT INFORMATION at the end of this labeling for the text of the separate leaflet provided for patients.

Laboratory Tests: No specific laboratory tests are recommended for monitoring patients prior to and/or after treatment with sumatriptan.

Drug Interactions: Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and sumatriptan within 24 hours of each other should be avoided (see CONTRAINDICATIONS).

MAO-A inhibitors reduce sumatriptan clearance, significantly increasing systemic exposure. Therefore, the use of IMITREX Nasal Spray in patients receiving MAO-A inhibitors is contraindicated (see CLINICAL PHARMACOLOGY and CONTRAINDICATIONS).

Selective serotonin reuptake inhibitors (SSRIs) (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) have been reported, rarely, to cause weakness, hyperreflexia, and incoordination when coadministered with sumatriptan. If concomitant treatment with sumatriptan and an SSRI is clinically warranted, appropriate observation of the patient is advised.

Drug/Laboratory Test Interactions: IMITREX Nasal Spray is not known to interfere with commonly employed clinical laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility: ***Carcinogenesis:*** In carcinogenicity studies, rats and mice were given sumatriptan by oral gavage (rats, 104 weeks) or drinking water (mice, 78 weeks). Average exposures achieved in mice receiving the highest dose (target dose of 160 mg/kg/day) were approximately 184 times the exposure attained in humans after the maximum recommended single intranasal dose of 20 mg. The highest dose administered to rats (160 mg/kg/day, reduced from 360 mg/kg/day during week 21) was approximately 78 times the maximum recommended single intranasal dose of 20 mg on a mg/m^2 basis. There was no evidence of an increase in tumors in either species related to sumatriptan administration. Local effects on nasal and respiratory tissue after chronic intranasal dosing in animals have not been evaluated (see WARNINGS).

Mutagenesis: Sumatriptan was not mutagenic in the presence or absence of metabolic activation when tested in 2 gene mutation assays (the Ames test and the in vitro mammalian Chinese hamster V79/HGPRT assay). In 2 cytogenetics assays (the in vitro human lymphocyte assay and the in vivo rat micronucleus assay) sumatriptan was not associated with clastogenic activity.

Impairment of Fertility: In a study in which male and female rats were dosed daily with oral sumatriptan prior to and throughout the mating period, there was a treatment-related decrease in fertility secondary to a decrease in mating in animals treated with 50 and 500 mg/kg/day. The highest no-effect dose for this finding was 5 mg/kg/day, or approximately twice the maximum recommended single human intranasal dose of 20 mg on a mg/m^2 basis. It is not clear whether the problem is associated with treatment of the males or females or both combined. In a similar study by the subcutaneous route there was no evidence of impaired fertility at 60 mg/kg/day, the maximum dose tested, which is equivalent to approximately 29 times the maximum recommended single human intranasal dose of 20 mg on a mg/m^2 basis. Fertility studies, in which sumatriptan was administered by the intranasal route, were not conducted.

Pregnancy: Pregnancy Category C. In reproductive toxicity studies in rats and rabbits, oral treatment with sumatriptan was associated with embryolethality, fetal abnormalities, and pup mortality. When administered by the intravenous route to rabbits, sumatriptan has been shown to be embryolethal. Reproductive toxicity studies for sumatriptan by the intranasal route have not been conducted.

There are no adequate and well-controlled studies in pregnant women. Therefore, IMITREX Nasal Spray should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In assessing this information, the following findings should be considered.

Embryolethality: When given orally or intravenously to pregnant rabbits daily throughout the period of organogenesis, sumatriptan caused embryolethality at doses at or close to those producing maternal toxicity. In the oral studies this dose was 100 mg/kg/day, and in the intravenous studies this dose was 2.0 mg/kg/day. The mechanism of the embryolethality is not known. The highest no-effect dose for embryolethality by the oral route was 50 mg/kg/day, which is approximately 48 times the maximum single recommended human intranasal dose of 20 mg on a mg/m^2 basis. By the intravenous route, the highest no-effect dose was 0.75 mg/kg/day, or approximately 0.7 times the maximum single recommended human intranasal dose of 20 mg on a mg/m^2 basis.

The intravenous administration of sumatriptan to pregnant rats throughout organogenesis at 12.5 mg/kg/day, the maximum dose tested, did not cause embryolethality. This dose is approximately 6 times the maximum single recommended human intranasal dose of 20 mg on a mg/m^2 basis. Additionally, in a study in rats given subcutaneous sumatriptan daily, prior to and throughout pregnancy, at 60 mg/kg/day, the maximum dose tested, there was no evidence of increased embryo/fetal lethality. This dose is equivalent to approximately 29 times the maximum recommended single human intranasal dose of 20 mg on a mg/m^2 basis.

Teratogenicity: Oral treatment of pregnant rats with sumatriptan during the period of organogenesis resulted in an increased incidence of blood vessel abnormalities (cervicothoracic and umbilical) at doses of approximately 250 mg/kg/day or higher. The highest no-effect dose was approximately 60 mg/kg/day, which is approximately 29 times the maximum single recommended human intranasal dose of 20 mg on a mg/m^2 basis. Oral treatment of pregnant rabbits with sumatriptan during the period of organogenesis resulted in an increased incidence of cervicothoracic vascular and skeletal abnormalities. The highest no-effect dose for these effects was 15 mg/kg/day, or approximately 14 times the maximum single recommended human intranasal dose of 20 mg on a mg/m^2 basis.

A study in which rats were dosed daily with oral sumatriptan prior to and throughout gestation demonstrated embryo/fetal toxicity (decreased body weight, decreased ossification, increased incidence of rib variations) and an increased incidence of a syndrome of malformations (short tail/short body and vertebral disorganization) at 500 mg/kg/day. The highest no-effect dose was 50 mg/kg/day, or approximately 24 times the maximum single recommended human intranasal dose of 20 mg on a mg/m^2 basis. In a study in rats dosed daily with subcutaneous sumatriptan prior to and throughout pregnancy, at a dose of 60 mg/kg/day, the maximum dose tested, there was no evidence of teratogenicity. This dose is equivalent to approximately 29 times the maximum recommended single human intranasal dose of 20 mg on a mg/m^2 basis.

Pup Deaths: Oral treatment of pregnant rats with sumatriptan during the period of organogenesis resulted in a decrease in pup survival between birth and postnatal day 4 at doses of approximately 250 mg/kg/day or higher. The highest no-effect dose for this effect was approximately 60 mg/kg/day, or 29 times the maximum single recommended human intranasal dose of 20 mg on a mg/m^2 basis. Oral treatment of pregnant rats with sumatriptan from gestational day 17 through postnatal day 21 demonstrated a decrease in pup survival measured at postnatal days 2, 4, and 20 at the dose of 1000 mg/kg/day. The highest no-effect dose for this finding was 100 mg/kg/day, approximately 49 times the maximum single recommended human intranasal dose of 20 mg on a mg/m^2 basis. In a similar study in rats by the subcutaneous route there was no increase in pup death at 81 mg/kg/day, the highest dose tested, which is equivalent to 40 times the maximum single recommended human intranasal dose of 20 mg on a mg/m^2 basis.

To monitor fetal outcomes of pregnant women exposed to IMITREX, GlaxoSmithKline maintains a Sumatriptan Pregnancy Registry. Physicians are encouraged to register patients by calling (800) 336-2176.

Nursing Mothers: Sumatriptan is excreted in human breast milk. Therefore, caution should be exercised when considering the administration of IMITREX Nasal Spray to a nursing woman.

Pediatric Use: Safety and effectiveness of IMITREX Nasal Spray in pediatric patients have not been established.

Completed placebo-controlled clinical trials evaluating oral sumatriptan (25 to 100 mg) in pediatric patients aged 12 to 17 years enrolled a total of 701 adolescent migraineurs. These studies did not establish the efficacy of oral sumatriptan compared to placebo in the treatment of migraine in adolescents. Adverse events observed in these clinical trials were similar in nature to those reported in clinical trials in adults. The frequency of all adverse events in these patients appeared to be both dose- and age-dependent, with younger patients reporting events more commonly than older adolescents. Postmarketing experience includes a limited number of reports that describe pediatric patients who have experienced adverse events, some clinically serious, after use of subcutaneous sumatriptan and/or oral sumatriptan. These reports include events similar in nature to those reported rarely in adults. A myocardial infarct has been reported in a 14-year-old male following the use of oral sumatriptan; clinical signs occurred within 1 day of drug administration. Since clinical data to determine the frequency of serious adverse events in pediatric patients who might receive injectable, oral, or intranasal sumatriptan are not presently available, the use of sumatriptan in patients aged younger than 18 years is not recommended.

Geriatric Use: The use of sumatriptan in elderly patients is not recommended because elderly patients are more likely to have decreased hepatic function, they are at higher risk for CAD, and blood pressure increases may be more pronounced in the elderly (see WARNINGS).

ADVERSE REACTIONS

Serious cardiac events, including some that have been fatal, have occurred following the use of IMITREX Injection or Tablets. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).