BULKY DOCUMENTS

(exceeds 300 pages)

Proceeding/Serial No: 91165803

Filed: 11-13-06

Title: Notice of Reliance

Part 1 **of** 2

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO THE COMMISSIONER FOR TRADEMARKS, P.O. BOX 1451, ALEXANDRIA, VA 22313-1451 ON THE DATE INDICATED BELOW

BY: _____

DATE: 11-7-06

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE TRADEMARK TRIAL AND APPEAL BOARD

BIOGEN IDEC INC.

Opposer,

TTAB

v.

Opposition No. 91,165,803

BIOGENESIS NUTRACEUTICALS, INC.
Applicant.

NOTICE OF RELIANCE

Honorable Commissioner for Trademarks
P.O. Box 1451
Alexandria, VA 22313-1451

Dear Commissioner:

Pursuant to T.B.M.P. §§704.03(b)(1)(B) and 704.08, and 37 C.F.R. §2.122(e), Opposer hereby gives notice that it intends to rely on the third-party registrations evidenced by copies of the printouts from the US PTO website attached hereto, and corresponding copies of pages from the Physician's Desk Reference For Prescription Drugs and Physician's Desk Reference For Nonprescription Drugs attached hereto, which are available to the general public in libraries or of general circulation among members of the public, or that segment of the public which is relevant to this proceeding, listed below which are relevant to show that companies (directly or through their affiliates or subsidiaries) manufacture, distribute, sell and/or promote both prescription and non-prescription pharmaceutical preparations and medicines.

Wyeth Pharmaceuticals:

Reg. No.	Mark	Prescription/Non Prescription
416,252	Benadryl	Nonprescription
1,803,595	Cortizone•10	Nonprescription
1,293,844	Nasalcrom	Nonprescription
591,597	Rolaids	Nonprescription
565,723	Sudafed	Nonprescription
2,767,460	Caduet	Prescription
3,030,324	Lyrica	Prescription
1,468,768	Norvasc	Prescription
1,702,392	Zithromax	Prescription
2,535,836	Zyrtec-D	Prescription

Novartis:

Reg. No.	Mark	Prescription/Non Prescription
83,823	Ex-lax	Nonprescription
1,567,931	Lamisil	Nonprescription
549,313	Maalox	Nonprescription
1,452,879	Theraflu	Nonprescription
2,791,532	Triaminic	Nonprescription
1,569,211	Cataflam	Prescription
1,265,560	Clozaril	Prescription
2,177,116	Diovan	Prescription
2,713,780	Enablex	Prescription
517,928	Ritalin	Prescription
2,696,669	Zelnorm	Prescription

Glaxosmithkline:

Reg. No.	Mark	Prescription/Non Prescription
2,464,248	Abreva	Nonprescription
1,316,519	Citrucel	Nonprescription
724,141	Contac	Nonprescription
828,755	Gaviscon	Nonprescription
722,166	Phazyme	Nonprescription
1,026,512	Tagamet	Nonprescription
2,317,064	Agenerase	Prescription
1,144,669	Augmentin	Prescription
1,269,595	Bactroban	Prescription
2,931,724	Boniva	Prescription
1,870,977	Flonase	Prescription
1,787,324	Imitrex	Prescription
1,821,952	Paxil	Prescription

Respectfully submitted,

Dated: 11/7/06

By: _____

Roberta Jacobs-Meadway
Jay K. Meadway
Patricia G. Cramer
BALLARD SPAHR ANDREWS & INGERSOLL, LLP
1735 Market Street – 51st Floor
Philadelphia, PA 19103
(215) 665-8500
ATTORNEYS FOR OPPOSER

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a true and correct copy of the attached Notice of Reliance filed with U.S. Trademark Trial and Appeal Board was served on counsel for the Applicant at the addresses and on the date listed below via the United States Postal Service as First Class Mail, postage pre-paid:

Paul Richard Brown, Esquire
BERESFORD BOOTH PLLC
145 Third Avenue South, Suite 200
Edmonds, WA 98020
paulb@beresfordlaw.com

Lawrence Graham, Esquire
BLACK LOWE & GRAHAM
701 Fifth Avenue, Suite 4800
Seattle, WA 98104
graham@blacklaw.com

Dated: Nov. 7th, 2006

Thank you for your request. Here are the latest results from the TARR web server.

This page was generated by the TARR system on 2006-06-27 20:24:56 ET

Serial Number: 71477895 Assignment Information

Registration Number: 416252 Assignment Information

Mark (words only): BENADRYL

Standard Character claim: No

Current Status: This registration has been renewed.

Date of Status: 2005-10-05

Filing Date: 1944-12-23

Transformed into a National Application: No

Registration Date: 1945-09-04

Register: Principal

Law Office Assigned: (NOT AVAILABLE)

If you are the applicant or applicant's attorney and have questions about this file, please contact the Trademark Assistance Center at TrademarkAssistanceCenter@uspto.gov

Current Location: M1D -TMO Law Office 110 - Docket Clerk

Date In Location: 2006-02-13

LAST APPLICANT(S)/OWNER(S) OF RECORD

1. WARNER-LAMBERT COMPANY LLC

Address:
WARNER-LAMBERT COMPANY LLC
201 TABOR ROAD
MORRIS PLAINS, NJ 07950
United States
Legal Entity Type: Ltd Liab Co
State or Country Where Organized: Delaware

GOODS AND/OR SERVICES

U.S. Class: 018 (International Class 005)
Class Status: Active

PHARMACEUTICAL PREPARATIONS CONTAINING DIPHENHYDAMINE HYDROCHLORIDE
Basis: 1(a)
First Use Date: 1944-11-27
First Use in Commerce Date: 1944-11-27

ADDITIONAL INFORMATION

(NOT AVAILABLE)

MADRID PROTOCOL INFORMATION

(NOT AVAILABLE)

PROSECUTION HISTORY

2005-11-15 - Undeliverable Mail - No Action Taken

2005-11-09 - Undeliverable Mail - No Action Taken

2005-10-17 - PAPER RECEIVED

2005-10-05 - Third renewal 10 year

2005-10-05 - Section 8 (10-year) accepted/ Section 9 granted

2005-09-29 - Assigned To Paralegal

2005-08-18 - Combined Section 8 (10-year)/Section 9 filed

2005-08-18 - Combined Section 8 (10-year)/Section 9 filed

2005-08-18 - TEAS Section 8 & 9 Received

1985-09-24 - Second renewal

1985-03-22 - Section 9 filed/check record for Section 8

CORRESPONDENCE INFORMATION

Correspondent
T. D. MOLITERNO, LEGAL DIVISION
WARNER-LAMBERT COMPANY
201 TABOR ROAD
MORRIS PLAINS, NJ 07950

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Physician's Desk Reference for Non-Prescription Drugs

Benadryl Allergy Ultratab Tablets(Pfizer Consumer Healthcare)

BODY:

Drug Facts:

Active Ingredient: Purpose:
(in each capsule)

Diphenhydramine HCl
25 mg ..... Antihistamine

Uses:

temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:
runny nosesneezingitchy, watery eyesitching of the nose or throat ztemporarily relieves these symptoms due to the common cold:
runny nosesneezing

Warnings:

Do not use with any other product containing diphenhydramine, even one used on skin.

Ask a doctor before use if you have:

glaucomatrouble urinating due to an enlarged prostate glanda breathing problem such as emphysema or chronic bronchitis

Ask a doctor or pharmacist before use if you are taking sedatives or tranquilizers

When using this product:

marked drowsiness may occuravoid alcoholic drinksalcohol, sedatives, and tranquilizers may increase drowsinessbe careful when driving a motor vehicle or operating machineryexcitability may occur, especially in children

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions:

take every 4 to 6 hoursdo not take more than 6 doses in 24 hours

adults and children 12 years of age and over	25 mg to 50 mg (1 to 2 capsules)
children 6 to under 12 years of age	12.5 mg ** to 25 mg (1 capsule)

children under 6 years of age	ask a doctor

**12.5 mg dosage strength is not available in this package. Do not attempt to break capsules.

Other Information:

store at 59 deg. to 77 deg. F in a dry placeprotect from light

Inactive Ingredients: Capsules: D&C red no. 28, FD&C blue no. 1, FD&C red no. 3, FD&C red no. 40, gelatin, glyceryl monooleate, lactose, magnesium stearate, and titanium dioxide. Printed with black edible ink.

Tablets: candelilla wax, crospovidone, dibasic calcium phosphate dihydrate, D&C red no. 27 aluminum lake, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, pregelatinized starch, stearic acid, and titanium dioxide.

Questions? call 1-800-524-2624 (English/Spanish), weekdays, 9 AM-5 PM EST

How Supplied: Benadryl tablets are supplied in boxes of 24 and 48, bottle of 100; capsules are supplied in boxes of 24 and 48.

PRODUCT PHOTO(S): NOTE: These photos can be used only for identification by shape, color, and imprint. They do not depict actual *or relative* size.

The product samples shown here have been supplied by the manufacturer and reproduced in full color by PDR as a quick-reference identification aid. While every effort has been made to assure accurate reproduction, please remember that any visual identification should be considered preliminary. In cases of poisoning or suspected overdosage, the drug's identity should be verified by chemical analysis.
See Image

LANGUAGE: ENGLISH

LOAD-DATE: February 11, 2005

Thank you for your request. Here are the latest results from the TARR web server.

This page was generated by the TARR system on 2006-06-27 20:25:36 ET

Serial Number: 74200311 Assignment Information

Registration Number: 1803595 Assignment Information

Mark

Cortizone·10

(words only): CORTIZONE-10

Standard Character claim: No

Current Status: This registration has been renewed.

Date of Status: 2003-05-25

Filing Date: 1991-09-03

Transformed into a National Application: No

Registration Date: 1993-11-09

Register: Principal

Law Office Assigned: LAW OFFICE 11

If you are the applicant or applicant's attorney and have questions about this file, please contact the Trademark Assistance Center at TrademarkAssistanceCenter@uspto.gov

Current Location: 900 -File Repository (Franconia)

Date In Location: 2003-06-03

LAST APPLICANT(S)/OWNER(S) OF RECORD

1. PFIZER INC.

Address:
PFIZER INC.
235 EAST 42ND STREET

NEW YORK, NY 10017
United States
Legal Entity Type: Corporation
State or Country of Incorporation: Delaware

GOODS AND/OR SERVICES

International Class: 005
Class Status: Active
medication for the relief of minor skin irritations
Basis: 1(a)
First Use Date: 1992-09-29
First Use in Commerce Date: 1992-09-29

ADDITIONAL INFORMATION

Prior Registration Number(s):
1562987

MADRID PROTOCOL INFORMATION

(NOT AVAILABLE)

PROSECUTION HISTORY

2003-05-25 - First renewal 10 year

2003-05-25 - Section 8 (10-year) accepted/ Section 9 granted

2003-01-27 - Combined Section 8 (10-year)/Section 9 filed

2003-01-27 - PAPER RECEIVED

1999-08-01 - Section 8 (6-year) accepted & Section 15 acknowledged

1999-02-23 - Section 8 (6-year) and Section 15 Filed

1993-11-09 - Registered - Principal Register

1993-08-13 - Allowed for Registration - Principal Register (SOU accepted)

1993-07-21 - Statement of use processing complete

1992-12-28 - Amendment to Use filed

1993-07-01 - Reinstated

1993-02-26 - Abandonment - No use statement filed

1992-08-25 - Notice of allowance - mailed

1992-06-02 - Published for opposition

1992-05-01 - Notice of publication

1991-12-09 - Approved for Pub - Principal Register (Initial exam)

1991-12-04 - Assigned To Examiner

CORRESPONDENCE INFORMATION

Correspondent
JANE UNGARO (Attorney of record)

JANE UNGARO
PFIZER INC
201 TABOR ROAD
MORRIS PLAINS, NJ 07950

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Physician's Desk Reference for Non-Prescription Drugs

Cortizone 10 Creme(Pfizer Consumer Healthcare)

BODY:

Drug Facts

Active Ingredient: Purpose:

Hydrocortisone 1% ..... Anti-itch

Uses:

temporarily relieves itching of minor skin irritations, inflammation, and rashes due to:eczemainsect bitescosmet-icspsoriasisdetergentssoapspoison ivy, oak, sumacjewelryseborrheic dermatitisand for external anal and genital itching

other uses of this product should be only under the advice and supervision of a doctor

Warnings:

For external use only

Do no use

for the treatment of diaper rash. Consult a doctor.in the genital area if you have a vaginal discharge. Consult a doctor.

When using this product

avoid contact with the eyesdo not exceed the recommended daily dosage unless directed by a doctordo not put directly in rectum by using fingers or any mechanical device

Stop use and ask a doctor if

rectal bleeding occurscondition worsens, or if symptoms persist for more than 7 days or clear up and occur again within a few days, and do not begin use of any other hydrocortisone product unless you have asked a doctor

Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Directions:

adults and children 2 years of age and older:apply to affected area not more than 3 to 4 times dailychildren under 2 years of age: do not use, ask a doctor

for external anal and genital itching, adults:when practical, clean the affected area with mild soap and warm water and rinse thoroughlygently dry by patting or blotting with toilet tissue or a soft cloth before applyingapply to affected area not more than 3 to 4 times dailychildren under 12 years of age: ask a doctor

Other Information: store at 15 deg. to 30 deg. C (59 deg. to 86 deg. F)

Inactive Ingredients: aloe barbadensis gel, aluminum sulfate, calcium acetate, cetearyl alcohol, glycerin, light mineral oil, maltodextrin, methylparaben, potato dextrin, propylparaben, purified water, sodium cetearyl sulfate, sodium lauryl sulfate, white petrolatum, and white wax

Questions? call 1-800-223-0182, Monday to Friday, 9 AM - 5 PM EST

How Supplied: CORTIZONE 10(R) creme: .5 oz., 1 oz. and 2 oz. tubes.

PRODUCT PHOTO(S): NOTE: These photos can be used only for identification by shape, color, and imprint. They do not depict actual *or relative* size.

The product samples shown here have been supplied by the manufacturer and reproduced in full color by PDR as a quick-reference identification aid. While every effort has been made to assure accurate reproduction, please remember that any visual identification should be considered preliminary. In cases of poisoning or suspected overdosage, the drug's identity should be verified by chemical analysis.
See Image

LANGUAGE: ENGLISH

LOAD-DATE: February 11, 2005

Thank you for your request. Here are the latest results from the TARR web server.

This page was generated by the TARR system on 2006-06-27 20:26:50 ET

Serial Number: 73426051 Assignment Information

Registration Number: 1293844 Assignment Information

Mark

Nasalcrom

(words only): NASALCROM

Standard Character claim: No

Current Status: This registration has been renewed.

Date of Status: 2004-09-20

Filing Date: 1983-05-16

Transformed into a National Application: No

Registration Date: 1984-09-11

Register: Principal

Law Office Assigned: (NOT AVAILABLE)

If you are the applicant or applicant's attorney and have questions about this file, please contact the Trademark Assistance Center at TrademarkAssistanceCenter@uspto.gov

Current Location: 900 -File Repository (Franconia)

Date In Location: 2004-09-24

LAST APPLICANT(S)/OWNER(S) OF RECORD

1. Pharmacia & Upjohn Company

Address:
Pharmacia & Upjohn Company
301 Henrietta Street

Kalamazoo, MI 49001
United States
Legal Entity Type: Corporation
State or Country of Incorporation: Delaware

GOODS AND/OR SERVICES

International Class: 005
Class Status: Active
Anti-Allergic Solution for the Prevention and Treatment of Allergic Rhinitis
Basis: 1(a)
First Use Date: 1982-12-20
First Use in Commerce Date: 1982-12-20

ADDITIONAL INFORMATION

Prior Registration Number(s):
1078233
1087892

MADRID PROTOCOL INFORMATION

(NOT AVAILABLE)

PROSECUTION HISTORY

2004-09-20 - First renewal 10 year

2004-09-20 - Section 8 (10-year) accepted/ Section 9 granted

2004-08-24 - Combined Section 8 (10-year)/Section 9 filed

2004-08-24 - Combined Section 8 (10-year)/Section 9 filed

2004-08-24 - TEAS Section 8 & 9 Received

2004-08-24 - TEAS Change Of Correspondence Received

1994-01-25 - Post Registration action correction

1990-05-15 - Section 8 (6-year) accepted & Section 15 acknowledged

1990-03-29 - Section 8 (6-year) and Section 15 Filed

1984-09-11 - Registered - Principal Register

1984-06-26 - Published for opposition

1984-05-02 - Notice of publication

1984-03-14 - Approved for Pub - Principal Register (Initial exam)

1984-01-20 - Communication received from applicant

1983-12-27 - Non-final action mailed

1983-12-12 - Assigned To Examiner

CORRESPONDENCE INFORMATION

Correspondent
Richard A. Friedman
Pfizer Inc.
Legal Dvision, 56/2
201 Tabor Road
Morris Plains NJ 07950
Phone Number: 973-385-2259
Fax Number: 973-385-3117

Domestic Representative
FROST & JACOBS

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Physician's Desk Reference for Non-Prescription Drugs

NasalCrom Nasal Spray(Pfizer Consumer Healthcare)

BODY:

Description: NASALCROM Nasal Spray contains a liquid formulation of cromolyn sodium that stabilizes mast cells that release histamine. NASALCROM is neither an antihistamine nor a decongestant nor a corticosteroid. In addition to treating nasal allergy symptoms, it decreases the allergic reaction by reducing the release of histamine, the trigger of allergy symptoms, from mast cells. NASALCROM has no known drug interactions and is safe to use with medications including other allergy medications.

Active Ingredient: (per spray) Cromolyn sodium 5.2mg

Indications: To prevent and relieve nasal symptoms of hay fever and other nasal allergies:

runny/itchy nose sneezing allergic stuffy nose

Directions:

parent or care provider must supervise the use of this product by young children. Adults and children 2 years and older:

spray once into each nostril. Repeat 3-4 times a day (every 4-6 hours). If needed, may be used up to 6 times a day.

use every day while in contact with the cause of your allergies (pollen, molds, pets, and dust)

to prevent nasal allergy symptoms, use before contact with the cause of your allergies. For best results, start using up to one week before contact.

if desired, you can use this product with other medications, including other allergy medications.

children under 2 years: Do not use unless directed by a doctor

Warnings:

Do not use if you are allergic to any of the ingredients

Ask a doctor before use if you have fever discolored nasal discharge sinus pain wheezing

When using this product it may take several days of use to notice an effect. Your best effect may not be seen for 1 to 2 weeks brief stinging or sneezing may occur right after use do not use to treat sinus infection, asthma, or cold symptoms do not share this bottle with anyone else as this may spread germs

Stop use and ask a doctor if

shortness of breath, wheezing, or chest tightness occurs hives or swelling of the mouth or throat occurs your symptoms worsen you have new symptoms your symptoms do not begin to improve within two weeks

you need to use more than 12 weeks

If pregnant or breast feeding ask a health professional before use.

Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Inactive Ingredients: benzalkonium chloride, edetate disodium, purified water

How Supplied: NASALCROM Nasal Spray is available in 13mL (100 metered sprays) and 26mL (200 metered sprays) sizes

Store between 20 deg.-25 deg. C (68 deg.-77 deg. F). Keep away from light.

LANGUAGE: ENGLISH

LOAD-DATE: February 11, 2005

Thank you for your request. Here are the latest results from the TARR web server.

This page was generated by the TARR system on 2006-06-27 20:28:29 ET

Serial Number: 71653424 Assignment Information

Registration Number: 591597 Assignment Information

Mark

(words only): ROLAIDS

Standard Character claim: No

Current Status: This registration has been renewed.

Date of Status: 2004-04-13

Filing Date: 1953-09-21

Transformed into a National Application: No

Registration Date: 1954-06-22

Register: Principal

Law Office Assigned: (NOT AVAILABLE)

If you are the applicant or applicant's attorney and have questions about this file, please contact the Trademark Assistance Center at TrademarkAssistanceCenter@uspto.gov

Current Location: 900 -File Repository (Franconia)

Date In Location: 2004-04-26

LAST APPLICANT(S)/OWNER(S) OF RECORD

1. WARNER-LAMBERT COMPANY LLC

Address:
WARNER-LAMBERT COMPANY LLC
201 TABOR ROAD

MORRIS PLAINS, NJ 07950
United States
Legal Entity Type: Ltd Liab Co
State or Country Where Organized: Delaware

GOODS AND/OR SERVICES

U.S. Class: 018 (International Class 005)
Class Status: Active
ANTACID MINTS
Basis: 1(a)
First Use Date: 1953-08-25
First Use in Commerce Date: 1953-08-25

ADDITIONAL INFORMATION

(NOT AVAILABLE)

MADRID PROTOCOL INFORMATION

(NOT AVAILABLE)

PROSECUTION HISTORY

2004-04-13 - Third renewal 10 year

2004-04-13 - Section 8 (10-year) accepted/ Section 9 granted

2004-03-26 - Combined Section 8 (10-year)/Section 9 filed

2004-03-26 - TEAS Section 8 & 9 Received

1994-07-14 - Second renewal 10 year

1994-06-06 - Section 9 filed/check record for Section 8

1974-06-22 - First renewal

CORRESPONDENCE INFORMATION

Correspondent
RICHARD A. FRIEDMAN (Attorney of record)

RICHARD A. FRIEDMAN
PFIZER INC.
LEGAL DIVISION BUILDING 56/2ND SOUTH
201 TABOR ROAD

MORRIS PLAINS NJ 07950

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Physician's Desk Reference for Non-Prescription Drugs

Rolaids Tablets(Pfizer Consumer Healthcare)

BODY:

Drug Facts:

Active Ingredients
(in each tablet): Purpose:

Calcium carbonate 550 mg ..... Antacid

Magnesium hydroxide 110 mg ..... Antacid

Uses: relieves: heartburn sour stomach acid indigestion upset stomach due to these symptoms

Warnings:

Ask a doctor or pharmacist before use if you are

presently taking a prescription drug. Antacids may interact with certain prescription drugs.do not take more than 12 tablets in a 24-hour period, or use the maximum dosage for more than 2 weeks, except under the advice and supervision of a physician.

Keep out of reach of children.

Directions

chew 2 to 4 tablets, hourly if needed

Other Information:

each tablet contains: calcium 220 mg and magnesium 45 mgstore at 59 deg. to 77 deg. F in a dry place

Inactive Ingredients: Peppermint and Spearmint Flavors: dextrose, flavoring, magnesium stearate, polyethylene glycol, pregelatinized starch and sucrose

Cherry Flavor: dextrose, flavoring, magnesium stearate, polyethylene glycol, pregelatinized starch, D&C red no. 27 aluminum lake, and sucrose

Actions: Rolaids(R) provides rapid neutralization of stomach acid. Each tablet has an acid-neutralizing capacity of 14.7 mEq and the ability to maintain the pH of stomach contents at 3.5 or greater for a significant period of time.

Dosage and Administration: Chew 2 to 4 tablets as symptoms occur. Repeat hourly if symptoms return, or as directed by a physician.

How Supplied: Rolaids(R) is available in 12-tablet rolls, 3-packs containing three 12-tablet rolls and in bottles containing 150 or 300 tablets.

PRODUCT PHOTO(S): NOTE: These photos can be used only for identification by shape, color, and imprint. They do not depict actual *or relative* size.

The product samples shown here have been supplied by the manufacturer and reproduced in full color by PDR as a quick-reference identification aid. While every effort has been made to assure accurate reproduction, please remember that any visual identification should be considered preliminary. In cases of poisoning or suspected overdosage, the drug's identity should be verified by chemical analysis.
See Image

LANGUAGE: ENGLISH

LOAD-DATE: February 11, 2005

Thank you for your request. Here are the latest results from the TARR web server.

This page was generated by the TARR system on 2006-06-27 20:29:17 ET

Serial Number: 71623397 Assignment Information

Registration Number: 565723 Assignment Information

Mark

SUDAFED

(words only): SUDAFED

Standard Character claim: No

Current Status: This registration has been renewed.

Date of Status: 2003-02-10

Filing Date: 1952-01-10

Transformed into a National Application: No

Registration Date: 1952-10-21

Register: Principal

Law Office Assigned: (NOT AVAILABLE)

If you are the applicant or applicant's attorney and have questions about this file, please contact the Trademark Assistance Center at TrademarkAssistanceCenter@uspto.gov

Current Location: 900 -File Repository (Franconia)

Date In Location: 2003-02-11

LAST APPLICANT(S)/OWNER(S) OF RECORD

1. WARNER-LAMBERT COMPANY

Address:
WARNER-LAMBERT COMPANY
201 TABOR ROAD LEGAL DIVISION, 56/2

MORRIS PLAINS, NJ
United States
Legal Entity Type: Corporation
State or Country of Incorporation: Delaware

GOODS AND/OR SERVICES

U.S. Class: 018 (International Class 005)
Class Status: Active
MEDICINAL PREPARATION INTENDED FOR USE AS A SYMPATHOMIMETIC
Basis: 1(a)
First Use Date: 1951-12-18
First Use in Commerce Date: 1951-12-18

ADDITIONAL INFORMATION

(NOT AVAILABLE)

MADRID PROTOCOL INFORMATION

(NOT AVAILABLE)

PROSECUTION HISTORY

2003-02-10 - Third renewal 10 year

2003-02-10 - Section 8 (10-year) accepted/ Section 9 granted

2002-10-25 - Combined Section 8 (10-year)/Section 9 filed

2002-10-25 - Section 9 filed/check record for Section 8

2002-10-25 - PAPER RECEIVED

2002-10-21 - PAPER RECEIVED

1992-10-07 - Second renewal 10 year

1992-08-24 - Section 9 filed/check record for Section 8

1972-10-21 - First renewal

CORRESPONDENCE INFORMATION

Correspondent
RICHARD A. FRIEDMAN
PFIZER INC.

201 TABOR ROAD
LEGAL DIVISION, 56/2
MORRIS PLAINS, NJ 07950

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Physician's Desk Reference for Non-Prescription Drugs

Sudafed Nasal Decongestant Tablets(Pfizer Consumer Healthcare)

BODY:

Drug Facts:

Active Ingredient:
(in each tablet) Purpose:

Pseudoephedrine HCl
30 mg ..... Nasal decongestant

Uses:

temporarily relieves nasal congestion due to the common cold, hay fever or other upper respiratory allergies, and nasal congestion associated with sinusitistemporarily relieves sinus congestion and pressure

Warnings:

Do not use if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.

Ask a doctor before use if you have:

heart diseasehigh blood pressurethyroid diseasediabetestrouble urinating due to an enlarged prostate gland

When using this product:

do not use more than directed

Stop use and ask a doctor if:

you get nervous, dizzy, or sleeplesssymptoms do not improve within 7 days or are accompanied by fever

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions:

take every 4 to 6 hoursdo not take more than 4 doses in 24 hours

adults and children 12 years of age and over	2 tablets
children 6 to under 12 years of age	1 tablet
children under 6 years of age	ask a doctor

Other Information:

store at 59 deg. to 77 deg. F in a dry place

Inactive Ingredients: Acacia, candelilla wax, corn starch, FD&C red no. 40 aluminum lake, FD&C yellow no. 6 aluminum lake, hypromellose, lactose monohydrate, magnesium stearate, pharmaceutical glaze, poloxamer 407, polyethylene glycol, polyethylene oxide, polysorbate 60, povidone, sodium benzoate, sodium lauryl sulfate, stearic acid, sucrose, talc, and titanium dioxide. Printed with edible black ink.

Questions? call 1-800-524-2624 (English/Spanish), weekdays, 9 AM - 5 PM EST

How Supplied: Boxes of 24, 48 and 96.

PRODUCT PHOTO(S): NOTE: These photos can be used only for identification by shape, color, and imprint. They do not depict actual *or relative* size.

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United States
Legal Entity Type: Limited Partnership
State or Country Where Organized: Netherlands

GOODS AND/OR SERVICES

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32 of 192 DOCUMENTS

Physician's Desk Reference for Prescription Drugs

Caduet Tablets(Pfizer)

BODY:

DESCRIPTION

CADUET[(R)] (amlodipine besylate and atorvastatin calcium) tablets combine the long-acting calcium channel blocker amlodipine besylate with the synthetic lipid-lowering agent atorvastatin calcium.

The amlodipine besylate component of CADUET is chemically described as 3-Ethyl-5-methyl (+/-)-2-(2-amino-ethoxy)methyl-4-(o-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate. Its empirical formula is C[20] H[25] ClN[2] O[5] *C[6] H[6] O[3] S.

The atorvastatin calcium component of CADUET is chemically described as R-(R*, R*)-2-(4-fluorophenyl)-(beta), dgr-di-hydroxy-5-(1-methylethyl)-3-phenyl-4-(phenylamino)car-bonyl-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. Its empirical formula is (C[33] H[34] FN[2] O[5])[2] Ca*3H[2] O.

The structural formulae for amlodipine besylate and atorvastatin calcium are shown below.

See Image

See Image

CADUET contains amlodipine besylate, a white to off-white crystalline powder, and atorvastatin calcium, also a white to off-white crystalline powder. Amlodipine besylate has a molecular weight of 567.1 and atorvastatin calcium has a molecular weight of 1209.42. Amlodipine besylate is slightly soluble in water and sparingly soluble in ethanol. Atorvastatin calcium is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile; slightly soluble in ethanol, and freely soluble in methanol.

CADUET tablets are formulated for oral administration in the following strength combinations:

Table 1. CADUET Tablet Strengths

	2.5 mg/ 10 mg	2.5 mg/ 20 mg	2.5 mg/ 40 mg	5 mg/ 10 mg	5 mg/ 20 mg	5 mg/ 40 mg	5 mg/ 80 mg	10 mg/ 10 mg	10 mg/ 20 mg	10 mg/ 40 mg	10 mg/ 80 mg
amlodipine equivalent (mg)	2.5	2.5	2.5	5	5	5	5	10	10	10	10
atorvastatin equivalent	10	20	40	10	20	40	80	10	20	40	80

Table 1. CADUET Tablet Strengths

(mg)

Each tablet also contains calcium carbonate, croscarmellose sodium, microcrystalline cellulose, pregelatinized starch, polysorbate 80, hydroxypropyl cellulose, purified water, colloidal silicon dioxide (anhydrous), magnesium stearate, Opadry[(R)] II White 85F28751 (polyvinyl alcohol, titanium dioxide, PEG 3000 and talc) or Opadry[(R)] II Blue 85F10919 (polyvinyl alcohol, titanium dioxide, PEG 3000, talc and FD&C blue #2). Combinations of atorvastatin with 2.5 mg and 5 mg amlodipine are film coated white, and combinations of atorvastatin with 10 mg amlodipine are film coated blue.

CLINICAL PHARMACOLOGY

Mechanism of Action

CADUET

CADUET is a combination of two drugs, a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) amlodipine (antihypertensive/antianginal agent) and an HMG-CoA reductase inhibitor atorvastatin (cholesterol lowering agent). The amlodipine component of CADUET inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. The atorvastatin component of CADUET is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol.

The Amlodipine Component of CADUET

Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected *in vitro* but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

The precise mechanisms by which amlodipine relieves angina have not been fully delineated, but are thought to include the following:

Exertional Angina: In patients with exertional angina, amlodipine reduces the total peripheral resistance (afterload) against which the heart works and reduces the rate pressure product, and thus myocardial oxygen demand, at any given level of exercise.

Vasospastic Angina: Amlodipine has been demonstrated to block constriction and restore blood flow in coronary arteries and arterioles in response to calcium, potassium epinephrine, serotonin, and thromboxane A[2] analog in experimental animal models and in human coronary vessels *in vitro* . This inhibition of coronary spasm is responsible for the effectiveness of amlodipine in vasospastic (Prinzmetal's or variant) angina.

The Atorvastatin Component of CADUET

Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-

density lipoprotein), and VLDL (very-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor.

Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk.

Epidemiologic inv

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Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C, and inversely with the level of HDL-C.

In animal models, atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL; atorvastatin also reduces LDL production and the number of LDL particles.

Atorvastatin reduces total-C, LDL-C, and apo B in patients with homozygous and heterozygous familial hypercholesterolemia (FH), nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. Atorvastatin also reduces VLDL-C and TG and produces variable increases in HDL-C and apolipoprotein A-1. Atorvastatin reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C in patients with isolated hypertriglyceridemia. Atorvastatin reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinemia.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate density lipoprotein (IDL), and remnants, can also promote atherosclerosis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

Pharmacokinetics and Metabolism

Absorption

Studies with amlodipine: After oral administration of therapeutic doses of amlodipine alone, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64% and 90%. The bioavailability of amlodipine when administered alone is not altered by the presence of food.

Studies with atorvastatin: After oral administration alone, atorvastatin is rapidly absorbed; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by Cmax and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for Cmax and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration (see DOSAGE AND ADMINISTRATION).

Studies with CADUET: Following oral administration of CADUET peak plasma concentrations of amlodipine and atorvastatin are seen at 6 to 12 hours and 1 to 2 hours post dosing, respectively. The rate and extent of absorption (bioavailability) of amlodipine and atorvastatin from CADUET are not significantly different from the bioavailability of amlodipine and atorvastatin administered separately (see above).

The bioavailability of amlodipine from CADUET was not affected by food. Although food decreases the rate and extent of absorption of atorvastatin from CADUET by approximately 32% and 11%, respectively, as it does with atorvastatin when given alone. LDL-C reduction is similar whether atorvastatin is given with or without food.

Distribution

Studies with amlodipine: Ex vivo studies have shown that approximately 93% of the circulating amlodipine drug is bound to plasma proteins in hypertensive patients. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

Studies with atorvastatin : Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is >/=98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin calcium is likely to be secreted in human milk (see CONTRAINDICATIONS , Pregnancy and Lactation , and PRECAUTIONS , Nursing Mothers).

Metabolism

Studies with amlodipine: Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism.

Studies with atorvastatin: Atorvastatin is extensively metabolized to ortho-and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho-and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following coadministration with erythromycin, a known inhibitor of this isozyme (see PRECAUTIONS , Drug Interactions). In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion

Studies with amlodipine: Elimination from the plasma is biphasic with a terminal elimination half-life of about 30-50 hours. Ten percent of the parent amlodipine compound and 60% of the metabolites of amlodipine are excreted in the urine.

Studies with atorvastatin: Atorvastatin and its me-tabolites are eliminated primarily in bile following he-patic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

Special Populations

Geriatric

Studies with amlodipine: Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40-60%, and a lower initial dose of amlodipine may be required.

Studies with atorvastatin: Plasma concentrations of atorvastatin are higher (approximately 40% for Cmax and 30% for AUC) in healthy elderly subjects (age >/=65 years) than in young adults. Clinical data suggest a greater degree of LDL-lowering at any dose of atorvastatin in the elderly population compared to younger adults (see PRECAUTIONS section, Geriatric Use).

Pediatric

Studies with amlodipine: Sixty-two hypertensive patients aged 6 to 17 years received doses of amlodipine between 1.25 mg and 20 mg. Weight-adjusted clearance and volume of distribution were similar to values in adults.

Studies with atorvastatin: Pharmacokinetic data in the pediatric population are not available.

Gender

Studies with atorvastatin: Plasma concentrations of atorvastatin in women differ from those in men (approximately 20% higher for Cmax and 10% lower for AUC); however, there is no clinically significant difference in LDL-C reduction with atorvastatin between men and women.

Renal Insufficiency

Studies with amlodipine: The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial amlodipine dose.

Studies with atorvastatin: Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin; thus, dose adjustment of atorvastatin in patients with renal dysfunction is not necessary (see DOSAGE AND ADMINISTRATION).

Hemodialysis

While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to significantly enhance clearance of atorvastatin and/or amlodipine since both drugs are extensively bound to plasma proteins.

Hepatic Insufficiency

Studies with amlodipine: Elderly patients and patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40-60%, and a lower initial dose may be required.

Studies with atorvastatin: In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. Cmax and AUC are each 4-fold greater in patients with Childs-Pugh A disease. Cmax and AUC of atorvastatin are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease (see CONTRAINDICATIONS).

Heart Failure

Studies with amlodipine: In patients with moderate to severe heart failure, the increase in AUC for amlodipine was similar to that seen in the elderly and in patients with hepatic insufficiency.

Pharmacodynamics

Hemodynamic Effects of Amlodipine: Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute intravenous administration of amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic administration of oral amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.

With chronic once daily oral administration of amlodipine, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105-114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90-104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressures (+1/-2 mmHg).

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when co-administered with beta-blockers to man. Similar findings, however, have been observed in normals or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

Electrophysiologic Effects of Amlodipine: Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving amlodipine and concomitant beta blockers. In clinical studies in which amlodipine was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed. In clinical trials with angina patients alone, amlodipine therapy did not alter electrocardiographic intervals or produce higher degrees of AV blocks.

LDL-C Reduction with Atorvastatin: Atorvastatin as well as some of its metabolites are pharmacologically active in humans. The liver is the primary site of action and the principal site of cholesterol synthesis and LDL clearance. Drug dosage rather than systemic drug concentration correlates better with LDL-C reduction. Individualization of drug dosage should be based on therapeutic response (see DOSAGE AND ADMINISTRATION).

Clinical Studies

Clinical Studies with Amlodipine

Amlodipine Effects in Hypertension

Adult Patients: The antihypertensive efficacy of amlodipine has been demonstrated in a total of 15 double-blind, placebo-controlled, randomized studies involving 800 patients on amlodipine and 538 on placebo. Once daily administration produced statistically significant placebo-corrected reductions in supine and standing blood pressures at 24 hours postdose, averaging about 12/6 mmHg in the standing position and 13/7 mmHg in the supine position in patients with mild to moderate hypertension. Maintenance of the blood pressure effect over the 24-hour dosing interval was observed, with little difference in peak and trough effect. Tolerance was not demonstrated in patients studied for up to 1 year. The 3 parallel, fixed doses, dose response studies showed that the reduction in supine and standing blood pressures was dose-related within the recommended dosing range. Effects on diastolic pressure were similar in young and older patients. The effect on systolic pressure was greater in older patients, perhaps because of greater baseline systolic pressure. Effects were similar in black patients and in white patients.

Pediatric Patients: Two-hundred sixty-eight hypertensive patients aged 6 to 17 years were randomized first to amlodipine 2.5 or 5 mg once daily for 4 weeks and then randomized again to the same dose or to placebo for another 4 weeks. Patients receiving 5 mg amlodipine at the end of 8 weeks had lower blood pressure than those secondarily randomized to placebo. The magnitude of the treatment effect is difficult to interpret, but it is probably less than 5 mmHg systolic on the 5 mg dose. Adverse events were similar to those seen in adults.

Amlodipine Effects in Chronic Stable Angina: The effectiveness of 5-10 mg/day of amlodipine in exercise-induced angina has been evaluated in 8 placebo-controlled, double-blind clinical trials of up to 6 weeks duration involving 1038 patients (684 amlodipine, 354 placebo) with chronic stable angina. In 5 of the 8 studies, significant increases in exercise time (bicycle or treadmill) were seen with the 10 mg dose. Increases in symptom-limited exercise time averaged 12.8% (63 sec) for amlodipine 10 mg, and averaged 7.9% (38 sec) for amlodipine 5 mg. Amlodipine 10 mg

also increased time to 1 mm ST segment deviation in several studies and decreased angina attack rate. The sustained efficacy of amlodipine in angina patients has been demonstrated over long-term dosing. In patients with angina, there were no clinically significant reductions in blood pressures (4/1 mmHg) or changes in heart rate (+0.3 bpm).

Amlodipine Effects in Vasospastic Angina: In a double-blind, placebo-controlled clinical trial of 4 weeks duration in 50 patients, amlodipine therapy decreased attacks by approximately 4/week compared with a placebo decrease of approximately 1/week ($p<0.01$). Two of 23 amlodipine and 7 of 27 placebo patients discontinued from the study due to lack of clinical improvement.

Amlodipine Effects in Patients with Congestive Heart Failure: Amlodipine has been compared to placebo in four 8-12 week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF. In a long-term (follow-up at least 6 months, mean 13.8 months) placebo-controlled mortality/morbidity study of amlodipine 5-10 mg in 1153 patients with NYHA classes III (n=931) or IV (n=222) heart failure on stable doses of diuretics, digoxin, and ACE inhibitors, amlodipine had no effect on the primary endpoint of the study which was the combined endpoint of all-cause mortality and cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure), or on NYHA classification, or symptoms of heart failure. Total combined all-cause mortality and cardiac morbidity events were 222/571 (39%) for patients on amlodipine and 246/583 (42%) for patients on placebo; the cardiac morbid events represented about 25% of the endpoints in the study.

Another study (PRAISE-2) randomized patients with NYHA class III (80%) or IV (20%) heart failure without clinical symptoms or objective evidence of underlying ischemic disease, on stable doses of ACE inhibitor (99%), digitalis (99%) and diuretics (99%), to placebo (n=827) or amlodipine (n=827) and followed them for a mean of 33 months. There was no statistically significant difference between amlodipine and placebo in the primary endpoint of all cause mortality (95% confidence limits from 8% reduction to 29% increase on amlodipine). With amlodipine there were more reports of pulmonary edema.

Clinical Studies with Atorvastatin

Prevention of Cardiovascular Disease: In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of atorvastatin on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients 40-80 years of age (mean of 63 years), without a previous myocardial infarction and with TC levels </=251 mg/dl (6.5 mmol/l). Additionally all patients had at least 3 of the following cardiovascular risk factors: male gender (81.1%), age >55 years (84.5%), smoking (33.2%), diabetes (24.3%), history of CHD in a first-degree relative (26%), TC:HDL >6 (14.3%), peripheral vascular disease (5.1%), left ventricular hypertrophy (14.4%), prior cerebrovascular event (9.8%), specific ECG abnormality (14.3%), proteinuria/albuminuria (62.4%) . In this double-blind, placebo-controlled study patients were treated with anti-hypertensive therapy (Goal BP <140/90 mm Hg for non-diabetic patients, <130/80 mm Hg for diabetic patients) and allocated to either atorvastatin 10 mg daily (n=5168) or placebo (n=5137), using a covariate adaptive method which took into account the distribution of nine baseline characteristics of patients already enrolled and minimized the imbalance of those characteristics across the groups. Patients were followed for a median duration of 3.3 years.

The effect of 10 mg/day of atorvastatin on lipid levels was similar to that seen in previous clinical trials.

Atorvastatin significantly reduced the rate of coronary events either fatal coronary heart disease (46 events in the placebo group vs 40 events in the atorvastatin group) or nonfatal MI (108 events in the placebo group vs 60 events in the atorvastatin group) with a relative risk reduction of 36% (based on incidences of 1.9% for atorvastatin vs 3.0% for placebo), p=0.0005 (see Figure 1) . The risk reduction was consistent regardless of age, smoking status, obesity or presence of renal dysfunction. The effect of atorvastatin was seen regardless of baseline LDL levels. Due to the small number of events, results for women were inconclusive.

See Image

Atorvastatin also significantly decreased the relative risk for revascularization procedures by 42% Although the reduction of fatal and non-fatal strokes did not reach a pre-defined significance level (p=0.01), a favorable trend was observed with a 26% relative risk reduction (incidences of 1.7% for atorvastatin and 2.3% for placebo). There was no significant difference between the treatment groups for death due to cardiovascular causes (p=0.51) or noncardiovascular causes (p=0.17).

Atorvastatin Studies in Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb *)* : Atorvastatin reduces total-C, LDL-C, VLDL-C, apo B, and TG, and increases HDL-C in patients with hypercholesterolemia and mixed dyslipidemia. Therapeutic response is seen within 2 weeks, and maximum response is usually achieved within 4 weeks and maintained during chronic therapy.

Atorvastatin is effective in a wide variety of patient populations with hypercholesterolemia, with and without hypertriglyceridemia, in men and women, and in the elderly.

In two multicenter, placebo-controlled, dose-response studies in patients with hypercholesterolemia, atorvastatin given as a single dose over 6 weeks significantly reduced total-C, LDL-C, apo B, and TG (pooled results are provided in Table 2).

Table 2. Dose-Response in Patients With Primary Hypercholesterolemia (Adjusted Mean Percent Change From Baseline)[a]

DOSE	N	TC	LDL-C	ApoB	TG	HDL-C	Non-HDL-C/HDL-C
Placebo	21	4	4	3	10	-3	7
10 mg	22	-29	-39	-32	-19	6	-34
20 mg	20	-33	-43	-35	-26	9	-41
40 mg	21	-37	-50	-42	-29	6	-45
80 mg	23	-45	-60	-50	-37	5	-53

[a] Results are pooled from 2 dose-response studies.

In patients with *Fredrickson* Types IIa and IIb hyperlipoproteinemia pooled from 24 controlled trials, the median (25[th] and 75[th] percentile) percent changes from baseline in HDL-C for atorvastatin 10, 20, 40, and 80 mg were 6.4 (-1.4, 14), 8.7 (0, 17), 7.8 (0, 16), and 5.1 (-2.7, 15), respectively. Additionally, analysis of the pooled data demonstrated consistent and significant decreases in total-C, LDL-C, TG, total-C/HDL-C, and LDL-C/HDL-C.

In three multicenter, double-blind studies in patients with hypercholesterolemia, atorvastatin was compared to other HMG-CoA reductase inhibitors. After randomization, patients were treated for 16 weeks with either atorvastatin 10 mg per day or a fixed dose of the comparative agent (Table 3).

Table 3. Mean Percent Change From Baseline at Endpoint (Double-Blind, Randomized, Active-Controlled Trials)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG	HDL-C	Non-HDL-C / HDL-C
Study 1							
Atorvastatin 10 mg	707	-27[a]	-36[a]	-28[a]	-17[a]	+7	-37[a]
Lovastati	191	-19	-27	-20	-6	+7	-28

Table 3. Mean Percent Change From Baseline at Endpoint (Double-Blind, Randomized, Active-Controlled Trials)

n 20 mg						
95% CI for Diff[1]		-9.2, -6.5	-10.7, -7.1	-10.0, -6.5	-15.2, -7.1	-1.7, 2.0	-11.1, -7.1
Study 2						
Atorvastatin 10 mg	222	-25[b]	-35[b]	-27[b]	-17[b]	+6	-36[b]
Pravastatin 20 mg	77	-17	-23	-17	-9	+8	-28
95% CI for Diff[1]		-10.8, -6.1	-14.5, -8.2	-13.4, -7.4	-14.1, -0.7	-4.9, 1.6	-11.5, -4.1
Study 3						
Atorvastatin 10 mg	132	-29[c]	-37[c]	-34[c]	-23[c]	+7	-39[c]
Simvastatin 10 mg	45	-24	-30	-30	-15	+7	-33
95% CI for Diff[1]		-8.7, -2.7	-10.1, -2.6	-8.0, -1.1	-15.1, -0.7	-4.3, 3.9	-9.6, -1.9

[1] A negative value for the 95% CI for the difference between treatments favors atorvastatin for all except HDL-C, for which a positive value favors atorvastatin. If the range does not include 0, this indicates a statistically significant difference.
[a] Significantly different from lovastatin, ANCOVA, p </=0.05
[b] Significantly different from pravastatin, ANCOVA, p </=0.05
[c] Significantly different from simvastatin, ANCOVA, p </=0.05

The impact on clinical outcomes of the differences in lipid-altering effects between treatments shown in Table 3 is not known. Table 3 does not contain data comparing the effects of atorvastatin 10 mg and higher doses of lovastatin, pravastatin, and simvastatin. The drugs compared in the studies summarized in the table are not necessarily interchangeable.

Atorvastatin Effects in Hypertriglyceridemia (Fredrickson Type IV *)* : The response to atorvastatin in 64 patients with isolated hypertriglyceridemia treated across several clinical trials is shown in the table below. For the atorvastatin-treated patients, median (min, max) baseline TG level was 565 (267-1502).

Table 4. Combined Patients With Isolated Elevated TG: Median (min, max) Percent Changes From Baseline

	Placebo (N=12)	Atorvastatin 10 mg (N=37)	Atorvastatin 20 mg (N=13)	Atorvastatin 80 mg (N=14)
Triglycerides	-12.4 (-36.6, 82.7)	-41.0 (-76.2, 49.4)	-38.7 (-62.7, 29.5)	-51.8 (-82.8, 41.3)
Total-C	-2.3 (-15.4, 24.4)	-28.2 (-44.9, -6.8)	-34.9 (-49.6, -15.2)	-44.4 (-63.5, -3.8)

Table 4. Combined Patients With Isolated Elevated TG: Median (min, max) Percent Changes From Baseline

LDL-C	3.6 (-31.3, 31.6)	-26.5 (-57.7, 9.8)	-30.4 (-53.9, 0.3)	-40.5 (-60.6, -13.8)
HDL-C	3.8 (-18.6, 13.4)	13.8 (-9.7, 61.5)	11.0 (-3.2, 25.2)	7.5 (-10.8, 37.2)
VLDL-C	-1.0 (-31.9, 53.2)	-48.8 (-85.8, 57.3)	-44.6 (-62.2, -10.8)	-62.0 (-88.2, 37.6)
non-HDL-C	-2.8 (-17.6, 30.0)	-33.0 (-52.1, -13.3)	-42.7 (-53.7, -17.4)	-51.5 (-72.9, -4.3)

Atorvastatin Effects in Dysbetalipoproteinemia (Fredrickson Type III *)* : The results of an open-label crossover study of atorvastatin in 16 patients (genotypes: 14 apo E2/E2 and 2 apo E3/E2) with dysbetalipoproteinemia (*Fredrickson* Type III) are shown in the table below.

Table 5. Open-Label Crossover Study of 16 Patients With Dysbetalipoproteinemia (Fredrickson Type III)

	Median (min, max) at Baseline (mg/dL)	Median % Change (min, max)	
		Atorvastatin 10 mg	Atorvastatin 80 mg
Total-C	442 (225, 1320)	-37 (-85, 17)	-58 (-90,-31)
Triglycerides	678 (273, 5990)	-39 (-92,-8)	-53 (-95,-30)
IDL-C + VLDL-C	215 (111, 613)	-32 (-76, 9)	-63 (-90,-8)
non-HDL-C	411 (218, 1272)	-43 (-87,-19)	-64 (-92,-36)

Atorvastatin Effects in Homozygous Familial Hypercholesterolemia: In a study without a concurrent control group, 29 patients ages 6 to 37 years with homozygous FH received maximum daily doses of 20 to 80 mg of atorvastatin. The mean LDL-C reduction in this study was 18%. Twenty-five patients with a reduction in LDL-C had a mean response of 20% (range of 7% to 53%, median of 24%); the remaining 4 patients had 7% to 24% increases in LDL-C. Five of the 29 patients had absent LDL-receptor function. Of these, 2 patients also had a portacaval shunt and had no significant reduction in LDL-C. The remaining 3 receptor-negative patients had a mean LDL-C reduction of 22%.

Atorvastatin Effects in Heterozygous Familial Hypercholesterolemic Pediatric Patients: In a double-blind, placebo-controlled study followed by an open-label phase, 187 boys and postmenarchal girls 10-17 years of age (mean age 14.1 years) with heterozygous FH or severe hypercholesterolemia were randomized to atorvastatin (n=140) or placebo (n=47) for 26 weeks and then all received atorvastatin for 26 weeks. Inclusion in the study required 1) a baseline LDL-C level >/= 190 mg/dL or 2) a baseline LDL-C >/= 160 mg/dL and positive family history of FH or documented premature cardiovascular disease in a first-or second-degree relative. The mean baseline LDL-C value was 218.6 mg/dL (range: 138.5-385.0 mg/dL) in the atorvastatin group compared to 230.0 mg/dL (range: 160.0-324.5 mg/dL) in placebo group. The dosage of atorvastatin (once daily) was 10 mg for the first 4 weeks and up-titrated to 20 mg if the LDL-C level was > 130 mg/dL. The number of atorvastatin-treated patients who required up-titration to 20 mg after Week 4 during the double-blind phase was 80 (57.1%).

Atorvastatin significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26 week double-blind phase (see Table 6).

Table 6. Lipid-altering Effects of Atorvastatin in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia or Severe Hypercholesterolemia (Mean Percent Change from Baseline at Endpoint in Intention-to-Treat Population)

DOSAGE	N	Total-C	LDL-C	HDL-C	TG	Apolipoprotein B
Placebo	47	-1.5	-0.4	-1.9	1.0	0.7
Atorvastatin	140	-31.4	-39.6	2.8	-12.0	-34.0

The mean achieved LDL-C value was 130.7 mg/dL (range: 70.0-242.0 mg/dL) in the atorvastatin group compared to 228.5 mg/dL (range: 152.0-385.0 mg/dL) in the placebo group during the 26 week double-blind phase.

The safety and efficacy of atorvastatin doses above 20 mg have not been studied in controlled trials in children. The long-term efficacy of atorvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

Clinical Study of Combined Amlodipine and Atorvastatin in Patients with Hypertension and Dyslipidemia

In a double-blind, placebo-controlled study, a total of 1660 patients with co-morbid hypertension and dyslipidemia received once daily treatment with eight dose combinations of amlodipine and atorvastatin (5/10, 10/10, 5/20, 10/20, 5/40, 10/40, 5/80, or 10/80 mg), amlodipine alone (5 mg or 10 mg), atorvastatin alone (10 mg, 20 mg, 40 mg, or 80 mg) or placebo. In addition to concomitant hypertension and dyslipidemia, 15% of the patients had diabetes mellitus, 22% were smokers and 14% had a positive family history of cardiovascular disease. At eight weeks, all eight combination-treatment groups of amlodipine and atorvastatin demonstrated statistically significant dose-related reductions in systolic blood pressure (SBP), diastolic blood pressure (DBP) and LDL-C compared to placebo, with no overall modification of effect of either component on SBP, DBP and LDL-C (Table 7).

Table 7. Efficacy in Terms of Reduction in Blood Pressure and LDL-C

Efficacy of the Combined Treatments in Reducing Systolic BP

Parameter / Analysis		ATO 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 0 mg	Mean Change (mmHg)	-3.0	-4.5	-6.2	-6.2	-6.4
	-	-1.5	-3.2	-3.2	-3.4	
AML 5 mg	Mean change (mmHg)	-12.8	-13.7	-15.3	-12.7	-12.2
	-9.8	-10.7	-12.3	-9.7	-9.2	
AML 10 mg	Mean change (mmHg)	-16.2	-15.9	-16.1	-16.3	-17.6
	-13.2	-12.9	-13.1	-13.3	-14.6	

Efficacy of the Combined Treatments in Reducing Diastolic BP

Parameter / Analysis		ATO 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 0 mg	Mean change	-3.3	-4.1	-3.9	-5.1	-4.1

Table 7. Efficacy in Terms of Reduction in Blood Pressure and LDL-C (mmHg)

	-	-0.8	-0.6	-1.8	-0.8	
AML 5 mg	Mean change (mmHg)	-7.6	-8.2	-9.4	-7.3	-8.4
	-4.3	-4.9	-6.1	-4.0	-5.1	
AML 10 mg	Mean change (mmHg)	-10.4	-9.1	-10.6	-9.8	-11.1
	-7.1	-5.8	-7.3	-6.5	-7.8	

Efficacy of the Combined Treatments in Reducing LDL-C (% change)

Parameter / Analysis		ATO 0 mg	ATO 10 mg	ATO 20 mg	ATO 40 mg	ATO 80 mg
AML 0 mg	Mean % change	-1.1	-33.4	-39.5	-43.1	-47.2
AML 5 mg	Mean % change	-0.1	-38.7	-42.3	-44.9	-48.4
AML 10 mg	Mean % change	-2.5	-36.6	-38.6	-43.2	-49.1

INDICATIONS AND USAGE

CADUET (amlodipine and atorvastatin) is indicated in patients for whom treatment with both amlodipine and atorvastatin is appropriate.

Amlodipine

Hypertension: Amlodipine is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents;*Chronic Stable Angina:* Amlodipine is indicated for the treatment of chronic stable angina. Amlodipine may be used alone or in combination with other antianginal or antihypertensive agents;*Vasospastic Angina (Prinzmetal's or Variant Angina):* Amlodipine is indicated for the treatment of confirmed or suspected vasospastic angina. Amlodipine may be used as monotherapy or in combination with other antianginal drugs.

AND

Atorvastatin

Prevention of Cardiovascular Disease: In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age >/= 55 years, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, atorvastatin is indicated to:
Reduce the risk of myocardial infarctionReduce the risk for revascularization procedures and angina*Heterozygous Familial and Nonfamilial Hypercholesterolemia:* Atorvastatin is indicated as an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (*Fredrickson* Types IIa and IIb);*Elevated Serum TG Levels:* Atorvastatin is indicated as an adjunct to diet for the treatment of patients with elevated serum TG levels (*Fredrickson* Type IV);*Primary Dysbetalipoproteinemia:* Atorvastatin is indicated for the treatment of patients with primary dysbetalipoproteinemia (*Fredrickson* Type III) who do not respond adequately to diet;*Homozygous Familial Hypercholesterolemia:* Atorvastatin is indicated to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable;*Pediatric Patients:* Atorvastatin is indicated as an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after

an adequate trial of diet therapy the following findings are present:

LDL-C remains >/= 190 mg/dL orLDL-C remains >/= 160 mg/dL and:
there is a positive family history of premature cardiovascular disease ortwo or more other CVD risk factors are present in the pediatric patients.

Therapy with lipid-altering agents should be a component of multiple-risk-factor intervention in individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lipid-altering agents should be used, in addition to a diet restricted in saturated fat and cholesterol, only when the response to diet and other nonpharmacological measures has been inadequate (see *National Cholesterol Education Program (NCEP) Guidelines,* summarized in Table 8).

Table 8. NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL-C Goal (mg/dL)	LDL-C Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL-C Level at Which to Consider Drug Therapy (mg/dL)
CHD[a] or CHD risk equivalents (10-year risk >20%)	<100	>/=100	>/=130 (100-129: drug optional)[b]
2+ Risk Factors (10-year risk </=20%)	<130	>/=130	10-year risk 10%-20%: >/=130 10-year risk <10%: >/=160
0-1 Risk Factor[c]	<160	>/=160	>/=190 (160-189: LDL-lowering drug optional)

[a] CHD, coronary heart disease
[b] Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.
[c] Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still >/= 200 mg/dL, non-HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

Prior to initiating therapy with atorvastatin, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, and alcoholism) should be excluded, and a lipid profile performed to measure total-C, LDL-C, HDL-C, and TG. For

patients with TG <400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation: LDL-C = total-C - (0.20 x TG + HDL-C). For TG levels >400 mg/dL (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation.

The antidyslipidemic component of CADUET has not been studied in conditions where the major lipoprotein abnormality is elevation of chylomicrons (*Fredrickson* Types I and V).

The NCEP classification of cholesterol levels in pediatric patients with a familial history of hypercholesterolemia or premature cardiovascular disease is summarized below:

Table 9. NCEP Classification of Cholesterol Levels in Pediatric Patients

Category	Total-C (mg/dL)	LDL-C (mg/dL)
Acceptable	<170	<110
Borderline	170-199	110-129
High	>/=200	>/=130

CONTRAINDICATIONS

CADUET contains atorvastatin and is therefore contraindicated in patients with active liver disease or unexplained persistent elevations of serum transaminases.

CADUET is contraindicated in patients with known hypersensitivity to any component of this medication.

Pregnancy and Lactation

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. CADUET, WHICH INCLUDES ATORVASTATIN, SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Increased Angina and/or Myocardial Infarction

Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

Liver Dysfunction

HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Persistent elevations (>3 times the upper limit of normal ULN occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.

In clinical trials in patients taking atorvastatin the following has been observed. One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients, with persistent LFT elevations continued treatment with a reduced dose of atorvastatin.

It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter . Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of CADUET is recommended.

CADUET should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of CADUET (see CONTRAINDICATIONS).

Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with the atorvastatin component of CADUET and with other drugs in the HMG-CoA reductase inhibitor class.

Uncomplicated myalgia has been reported in atorvastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values > 10 times ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CADUET therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with drugs in the HMG-CoA reductase inhibitor class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, or azole antifungals. Physicians considering combined therapy with CADUET and fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-lowering doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

In patients taking CADUET, therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

PRECAUTIONS

General

Since the vasodilation induced by the amlodipine component of CADUET is gradual in onset, acute hypotension has rarely been reported after oral administration of amlodipine. Nonetheless, caution should be exercised when administering CADUET as with any other peripheral vasodilator particularly in patients with severe aortic stenosis.

Before instituting therapy with CADUET, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE).

Use in Patients with Congestive Heart Failure

In general, calcium channel blockers should be used with caution in patients with heart failure. The amlodipine component of CADUET (5-10 mg per day) has been studied in a placebo-controlled trial of 1153 patients with NYHA Class III or IV heart failure (see CLINICAL PHARMACOLOGY) on stable doses of ACE inhibitor, digoxin, and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure). Amlodipine has been compared to placebo in four 8-12 week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF.

Beta-Blocker Withdrawal

The amlodipine component of CADUET is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker.

Endocrine Function

HMG-CoA reductase inhibitors, such as the atorvastatin component of CADUET interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if an HMG-CoA reductase inhibitor is administered concomitantly with drugs thatmay decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

CNS Toxicity

Studies with atorvastatin: Brain hemorrhage was seen in a female dog treated with atorvastatin calcium for 3 months at a dose equivalent to 120 mg atorvastatin/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses of atorvastatin calcium equivalent to up to 280 mg atorvastatin/kg/day. The 120 mg/kg dose of atorvastatin resulted in a systemic exposure approximately 16 times the human plasma area-under-the-curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated with atorvastatin calcium at a dose equivalent to 10 mg atorvastatin/kg/day and one at a dose equivalent to 120 mg atorvastatin/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses of atorvastatin calcium equivalent to up to 400 mg atorvastatin/kg/day or in rats at doses equivalent to up to 100 mg atorvastatin/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0-24) based on the maximum recommended human dose of 80 mg atorvastatin/day.

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of the HMG-CoA reductase class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose.

Information for Patients

Due to the risk of myopathy with drugs of the HMG-CoA reductase class, to which the atorvastatin component of CADUET belongs, patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Drug Interactions

Data from a drug-drug interaction study involving 10 mg of amlodipine and 80 mg of atorvastatin in healthy subjects indicate that the pharmacokinetics of amlodipine are not altered when the drugs are coadministered. The effect of amlodipine on the pharmacokinetics of atorvastatin showed no effect on the Cmax: 91% (90% confidence interval: 80 to 103%), but the AUC of atorvastatin increased by 18% (90% confidence interval: 109 to 127%) in the presence of amlodipine.

No drug interaction studies have been conducted with CADUET and other drugs, although studies have been conducted in the individual amlodipine and atorvastatin components, as described below:

Studies with Amlodipine:

In vitro data in human plasma indicate that amlodipine has no effect on the protein binding of drugs tested (digoxin, phenytoin, warfarin, and indomethacin).

Cimetidine : Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.

Maalox[(R)] (antacid): Co-administration of the antacid Maalox with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

Sildenafil : A single 100 mg dose of sildenafil (Viagra[(R)]) in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Digoxin: Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

Ethanol (alcohol): Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.

Warfarin: Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

Studies with Atorvastatin:

The risk of myopathy during treatment with drugs of the HMG-CoA reductase class is increased with concurrent administration of cyclosporine, fibric acid derivatives, niacin (nicotinic acid), erythromycin, or azole antifungals (see WARNINGS , Skeletal Muscle).

Antacid: When atorvastatin and Maalox TC suspension were coadministered, plasma concentrations of atorvastatin decreased approximately 35%. However, LDL-C reduction was not altered.

Antipyrine: Because atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Colestipol: Plasma concentrations of atorvastatin decreased approximately 25% when colestipol and atorvastatin were coadministered. However, LDL-C reduction was greater when atorvastatin and colestipol were coadministered than when either drug was given alone.

Cimetidine: Atorvastatin plasma concentrations and LDL-C reduction were not altered by coadministration of cimetidine.

Digoxin: When multiple doses of atorvastatin and digoxin were coadministered, steady-state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately.

Erythromycin: In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with coadministration of atorvastatin and erythromycin, a known inhibitor of cytochrome P450 3A4 (see WARNINGS , Skeletal Muscle).

Oral Contraceptives: Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking CADUET.

Warfarin: Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

Drug/Laboratory Test Interactions

None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies with amlodipine: Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg amlodipine/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m[2] basis, similar to the maximum recommended human dose of 10 mg amlodipine/day [*] . For the rat, the highest dose level was, on a mg/m[2] basis, about twice the maximum recommended human dose [*] .

Mutagenicity studies conducted with amlodipine maleate revealed no drug related effects at either the gene or chromosome levels.

There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg amlodipine/kg/day (8 times [*] the maximum recommended human dose of 10 mg/day on a mg/m[2] basis).

Studies with atorvastatin: In a 2-year carcinogenicity study with atorvastatin calcium in rats at dose levels equivalent to 10, 30, and 100 mg atorvastatin/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose.

A 2-year carcinogenicity study in mice given atorvastatin calcium at dose levels equivalent to 100, 200, and 400 mg atorvastatin/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose.

In vitro , atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli* , the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse micronucleus test.

There were no effects on fertility when rats were given atorvastatin calcium at doses equivalent to up to 175 mg atorvastatin/kg/day (15 times the human exposure). There was aplasia and aspermia in the epididymides of 2 of 10 rats treated with atorvastatin calcium at a dose equivalent to 100 mg atorvastatin/kg/day for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg/day and epididymal weight was lower at 100 mg/kg/day. Male rats given the equivalent of 100 mg atorvastatin/kg/day for 11 weeks prior to mating

had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of atorvastatin calcium equivalent to 10, 40, or 120 mg atorvastatin/kg/day for two years.

Pregnancy

Pregnancy Category X (see CONTRAINDICATIONS)

Safety in pregnant women has not been established with CADUET. CADUET should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking CADUET, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Studies with amlodipine: No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate at doses up to 10 mg amlodipine/kg/day (respectively 8 times [*] and 23 times [*] the maximum recommended human dose of 10 mg/day on a mg/m[2] basis) during their respective periods of major organogenesis. However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats receiving amlodipine maleate at 10 mg amlodipine/kg/day for 14 days before mating and throughout mating and gestation. Amlodipine maleate has been shown to prolong both the gestation period and the duration of labor in rats at this dose. There are no adequate and well-controlled studies in pregnant women. [*] Based on patient weight of 50 kg.

Studies with atorvastatin: Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses of atorvastatin calcium equivalent to up to 300 mg atorvastatin/kg/day or in rabbits at doses of atorvastatin calcium equivalent to up to 100 mg atorvastatin/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m[2]).

In a study in rats given atorvastatin calcium at doses equivalent to 20, 100, or 225 mg atorvastatin/kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity for pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on days 4 and 21 for pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye opening at 225 mg/kg/day). These doses of atorvastatin correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day.

Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took lovastatin with dextroamphetamine sulfate during the first trimester of pregnancy.

Labor and Delivery

No studies have been conducted in pregnant women on the effect of CADUET, amlodipine or atorvastatin on the mother or the fetus during labor or delivery, or on the duration of labor or delivery. Amlodipine has been shown to prolong the duration of labor in rats.

Nursing Mothers

It is not known whether the amlodipine component of CADUET is excreted in human milk. Nursing rat pups taking atorvastatin had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Because of the potential for adverse reactions in nursing infants, women taking CADUET should not breast-feed (see CONTRAINDICATIONS).

Pediatric Use

There have been no studies conducted to determine the safety or effectiveness of CADUET in pediatric populations.

Studies with amlodipine: The effect of amlodipine on blood pressure in patients less than 6 years of age is not known.

Studies with atorvastatin: Safety and effectiveness in patients 10–17 years of age with heterozygous familial hypercholesterolemia have been evaluated in controlled clinical trials of 6 months duration in adolescent boys and postmenarchal girls. Patients treated with atorvastatin had an adverse experience profile generally similar to that of patients treated with placebo, the most common adverse experiences observed in both groups, regardless of causality assessment, were infections. Doses greater than 20 mg have not been studied in this patient population. In this limited controlled study, there was no detectable effect on growth or sexual maturation in boys or on menstrual cycle length in girls. See CLINICAL PHARMACOLOGY , Clinical Studies section; ADVERSE REACTIONS , *Pediatric Patients* ; and DOSAGE AND ADMINISTRATION , *Pediatric Patients (10–17 years of age) with Heterozygous Familial Hypercholesterolemia* . Adolescent females should be counseled on appropriate contraceptive methods while on atorvastatin therapy (see CONTRAINDICATIONS and PRECAUTIONS , Pregnancy). Atorvastatin has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age.

Clinical efficacy with doses of atorvastatin up to 80 mg/day for 1 year have been evaluated in an uncontrolled study of patients with homozygous FH including 8 pediatric patients. See CLINICAL PHARMACOLOGY , Clinical Studies , *Atorvastatin Effects in Homozygous Familial Hypercholesterolemia* .

Geriatric Use

There have been no studies conducted to determine the safety or effectiveness of CADUET in geriatric populations.

In studies with amlodipine: Clinical studies of amlodipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection of the amlodipine component of CADUET for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40–60%, and a lower initial dose may be required (see DOSAGE AND ADMINISTRATION).

In studies with atorvastatin: The safety and efficacy of atorvastatin (10–80 mg) in the geriatric population (>/=65 years of age) was evaluated in the ACCESS study. In this 54-week open-label trial 1,958 patients initiated therapy with atorvastatin calcium 10 mg. Of these, 835 were elderly (>/=65 years) and 1,123 were non-elderly. The mean change in LDL-C from baseline after 6 weeks of treatment with atorvastatin calcium 10 mg was-38.2% in the elderly patients versus-34.6% in the non-elderly group.

The rates of discontinuation in patients on atorvastatin due to adverse events were similar between the two age groups. There were no differences in clinically relevant laboratory abnormalities between the age groups.

ADVERSE REACTIONS

CADUET

CADUET (amlodipine besylate/atorvastatin calcium) has been evaluated for safety in 1092 patients in double-blind placebo controlled studies treated for co-morbid hypertension and dyslipidemia. In general, treatment with CADUET was well tolerated. For the most part, adverse experiences have been mild or moderate in severity. In clinical trials with CADUET, no adverse experiences peculiar to this combination have been observed. Adverse experiences are similar in terms of nature, severity, and frequency to those reported previously with amlodipine and atorvastatin.

The following information is based on the clinical experience with amlodipine and atorvastatin.

The Amlodipine Component of CADUET

Amlodipine has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. In general, treatment with amlodipine was well tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with amlodipine were of mild or moderate severity. In controlled clinical trials directly comparing amlodipine (N=1730) in doses up to 10 mg to placebo (N=1250), discontinuation of amlodipine due to adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). The most common side effects are headache and edema. The incidence (%) of side effects which occurred in a dose related manner are as follows:

Adverse Event	amlodipine			
	2.5 mg N=275	5.0 mg N=296	10.0 mg N=268	Placebo N=520
Edema	1.8	3.0	10.8	0.6
Dizziness	1.1	3.4	3.4	1.5
Flushing	0.7	1.4	2.6	0.0
Palpitation	0.7	1.4	4.5	0.6

Other adverse experiences which were not clearly dose related but which were reported with an incidence greater than 1.0% in placebo-controlled clinical trials include the following:

Placebo-Controlled Studies

Adverse Event	amlodipine (%) (N=1730)	Placebo (%) (N=1250)
Headache	7.3	7.8
Fatigue	4.5	2.8
Nausea	2.9	1.9
Abdominal Pain	1.6	0.3
Somnolence	1.4	0.6

For several adverse experiences that appear to be drug and dose related, there was a greater incidence in women than men associated with amlodipine treatment as shown in the following table:

Adverse Event	amlodipine		Placebo	
	M=% (N=1218)	F=% (N=512)	M=% (N=914)	F=% (N=336)
Edema	5.6	14.6	1.4	5.1
Flushing	1.5	4.5	0.3	0.9
Palpitations	1.4	3.3	0.9	0.9
Somnolence	1.3	1.6	0.8	0.3

The following events occurred in </=1% but >0.1% of patients treated with amlodipine in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis.

Central and Peripheral Nervous System: hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo.

Gastrointestinal: anorexia, constipation, dyspepsia, ** dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia.

General: allergic reaction, asthenia, ** back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease.

Musculoskeletal System: arthralgia, arthrosis, muscle cramps, ** myalgia.

Psychiatric: sexual dysfunction (male ** and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.

Respiratory System: dyspnea, ** epistaxis.

Skin and Appendages: angioedema, erythema multi-forme, pruritus, ** rash, ** rash erythematous, rash maculopapular. **These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

Special Senses: abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.

Urinary System: micturition frequency, micturition disorder, nocturia.

Autonomic Nervous System: dry mouth, sweating increased.

Metabolic and Nutritional: hyperglycemia, thirst.

Hemopoietic: leukopenia, purpura, thrombocytopenia.

The following events occurred in </=0.1% of patients treated with amlodipine in controlled clinical trials or under conditions of open trials or marketing experience: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia.

Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina.

Amlodipine therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine.

The following postmarketing event has been reported infrequently with amlodipine treatment where a causal relationship is uncertain: gynecomastia. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis) in some cases severe enough to require hospitalization have been reported in association with use of amlodipine.

Amlodipine has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles.

The Atorvastatin Component of CADUET

Atorvastatin is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies of 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to atorvastatin calcium. The most frequent adverse events thought to be related to atorvastatin calcium were constipation, flatulence, dyspepsia, and abdominal pain.

Clinical Adverse Experiences

Adverse experiences reported in >/=2% of patients in placebo-controlled clinical studies of atorvastatin, regardless of causality assessment, are shown in Table 10.

Table 10. Adverse Events in Placebo-Controlled Studies (% of Patients)

Body System/ Adverse Event	Placebo N=270	atorvastatin			
		10 mg N=863	20 mg N=36	40 mg N=79	80 mg N=94
BODY AS A WHOLE					
Infection	10.0	10.3	2.8	10.1	7.4
Headache	7.0	5.4	16.7	2.5	6.4
Accidental Injury	3.7	4.2	0.0	1.3	3.2
Flu Syndrome	1.9	2.2	0.0	2.5	3.2
Abdominal Pain	0.7	2.8	0.0	3.8	2.1
Back Pain	3.0	2.8	0.0	3.8	1.1
Allergic Reaction	2.6	0.9	2.8	1.3	0.0
Asthenia	1.9	2.2	0.0	3.8	0.0
DIGESTIVE SYSTEM					
Constipation	1.8	2.1	0.0	2.5	1.1
Diarrhea	1.5	2.7	0.0	3.8	5.3
Dyspepsia	4.1	2.3	2.8	1.3	2.1
Flatulence	3.3	2.1	2.8	1.3	1.1
RESPIRATORY SYSTEM					
Sinusitis	2.6	2.8	0.0	2.5	6.4
Pharyngitis	1.5	2.5	0.0	1.3	2.1
SKIN AND APPENDAGES					
Rash	0.7	3.9	2.8	3.8	1.1

Table 10. Adverse Events in Placebo-Controlled Studies (% of Patients)

MUSCULOSKELETAL SYSTEM					
Arthralgia	1.5	2.0	0.0	5.1	0.0
Myalgia	1.1	3.2	5.6	1.3	0.0

Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)

In ASCOT (see CLINICAL PHARMACOLOGY , Clinical Studies , *Clinical Studies with Atorvastatin*) involving 10,305 participants treated with atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with atorvastatin was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up.

The following adverse events were reported, regardless of causality assessment, in patients treated with atorvastatin in clinical trials. The events in italics occurred in >/=2% of patients and the events in plain type occurred in <2% of patients.

Body as a Whole: *Chest pain* , face edema, fever, neck rigidity, malaise, photosensitivity reaction, generalized edema.

Digestive System: *Nausea* , gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice.

Respiratory System: *Bronchitis, rhinitis* , pneumonia, dyspnea, asthma, epistaxis.

Nervous System: *Insomnia, dizziness* , paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, peripheral neuropathy, torticollis, facial paralysis, hyperkinesia, depression, hypesthesia, hypertonia.

Musculoskeletal System: *Arthritis* , leg cramps, bursitis, tenosynovitis, myasthenia, tendinous contracture, myositis.

Skin and Appendages: Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, eczema, seborrhea, skin ulcer.

Urogenital System: *Urinary tract infection* , urinary frequency, cystitis, hematuria, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, albuminuria, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage.

Special Senses: Amblyopia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, parosmia, taste loss, taste perversion.

Cardiovascular System: Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arrhythmia, angina pectoris, hypertension.

Metabolic and Nutritional Disorders: *Peripheral edema* , hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia.

Hemic and Lymphatic System: Ecchymosis, anemia, lymphadenopathy, thrombocytopenia, petechia.

Postintroduction Reports with Atorvastatin

Adverse events associated with atorvastatin therapy reported since market introduction, that are not listed above,

regardless of causality assessment, include the following: anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), and rhabdomyolysis.

Pediatric Patients (ages 10-17 years)

In a 26-week controlled study in boys and postmenarchal girls (n=140), the safety and tolerability profile of atorvastatin 10 to 20 mg daily was generally similar to that of placebo (see CLINICAL PHARMACOLOGY , Clinical Studies section and PRECAUTIONS , Pediatric Use).

OVERDOSAGE

There is no information on overdosage with CADUET in humans.

Information on Amlodipine

Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg in dogs (11 or more times the maximum recommended clinical dose on a mg/m[2] basis) caused a marked peripheral vasodilation and hypotension.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of amlodipine is limited. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) was hospitalized, underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A patient who took 70 mg amlodipine and an unknown quantity of benzodiazepine in a suicide attempt developed shock which was refractory to treatment and died the following day with abnormally high benzodiazepine plasma concentration. A case of accidental drug overdose has been documented in a 19-month-old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae were noted.

If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

Information on Atorvastatin

There is no specific treatment for atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

DOSAGE AND ADMINISTRATION

Dosage of CADUET must be individualized on the basis of both effectiveness and tolerance for each individual component in the treatment of hypertension/angina and hyperlipidemia.

Amlodipine (Hypertension or angina)

Adults: The usual initial antihypertensive oral dose of amlodipine is 5 mg once daily with a maximum dose of 10 mg once daily. Small, fragile, or elderly individuals, or patients with hepatic insufficiency may be started on 2.5 mg once daily and this dose may be used when adding amlodipine to other antihypertensive therapy.

Dosage should be adjusted according to each patient's need. In general, titration should proceed over 7 to 14 days so that the physician can fully assess the patient's response to each dose level. Titration may proceed more rapidly, however, if clinically warranted, provided the patient is assessed frequently.

The recommended dose of amlodipine for chronic stable or vasospastic angina is 5–10 mg, with the lower dose suggested in the elderly and in patients with hepatic insufficiency. Most patients will require 10 mg for adequate effect. See ADVERSE REACTIONS section for information related to dosage and side effects.

Children: The effective antihypertensive oral dose of amlodipine in pediatric patients ages 6–17 years is 2.5 mg to 5 mg once daily. Doses in excess of 5 mg daily have not been studied in pediatric patients. See CLINICAL PHARMACOLOGY .

Atorvastatin (Hyperlipidemia)

The patient should be placed on a standard cholesterol-lowering diet before receiving atorvastatin and should continue on this diet during treatment with atorvastatin.

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb *)*

The recommended starting dose of atorvastatin is 10 or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of atorvastatin is 10 to 80 mg once daily. Atorvastatin can be administered as a single dose at any time of the day, with or without food. The starting dose and maintenance doses of atorvastatin should be individualized according to patient characteristics such as goal of therapy and response (see *NCEP Guidelines* , summarized in Table 8). After initiation and/or upon titration of atorvastatin, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.

Since the goal of treatment is to lower LDL-C, the NCEP recommends that LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should total-C be used to monitor therapy.

Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10–17 years of age)

The recommended starting dose of atorvastatin is 10 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in this patient population). Doses should be individualized according to the recommended goal of therapy (see NCEP Pediatric Panel Guidelines [1] , CLINICAL PHARMACOLOGY , and INDICATIONS AND USAGE). Adjustments should be made at intervals of 4 weeks or more.

Homozygous Familial Hypercholesterolemia

The dosage of atorvastatin in patients with homozygous FH is 10 to 80 mg daily. Atorvastatin should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable. Note: a 2.5/80 mg CADUET tablet is not available. Management of patients needing a 2.5/80 mg combination requires individual assessments of dyslipidemia and therapy with the individual components as a 2.5/80 mg CADUET tablet is not available.[1] National Cholesterol Education Program (NCEP): Highlights of the Report of the Expert Panel on Blood Cholesterol Levels in Children Adolescents. *Pediatrics* . 89(3):495-501. 1992.

Concomitant Therapy

Atorvastatin may be used in combination with a bile acid binding resin for additive effect. The combination of HMG-CoA reductase inhibitors and fibrates should generally be avoided (see WARNINGS , Skeletal Muscle , and PRECAUTIONS , Drug Interactions for other drug-drug interactions).

Dosage in Patients With Renal Insufficiency

Renal disease does not affect the plasma concentrations nor LDL-C reduction of atorvastatin; thus, dosage adjustment in patients with renal dysfunction is not necessary (see CLINICAL PHARMACOLOGY , Pharmacokinetics).

CADUET

CADUET may be substituted for its individually titrated components. Patients may be given the equivalent dose of CADUET or a dose of CADUET with increased amounts of amlodipine, atorvastatin or both for additional antianginal effects, blood pressure lowering, or lipid lowering effect.

CADUET may be used to provide additional therapy for patients already on one of its components. As initial therapy for one indication and continuation of treatment of the other, the recommended starting dose of CADUET should be selected based on the continuation of the component being used and the recommended starting dose for the added monotherapy.

CADUET may be used to initiate treatment in patients with hyperlipidemia and either hypertension or angina. The recommended starting dose of CADUET should be based on the appropriate combination of recommendations for the monotherapies. The maximum dose of the amlodipine component of CADUET is 10 mg once daily. The maximum dose of the atorvastatin component of CADUET is 80 mg once daily.

See above for detailed information related to the dosing and administration of amlodipine and atorvastatin.

HOW SUPPLIED

CADUET[(R)] tablets contain amlodipine besylate and atorvastatin calcium equivalent to amlodipine and atorvastatin in the dose strengths described below.

CADUET tablets are differentiated by tablet color/size and are engraved with "Pfizer" on one side and a unique number on the other side. CADUET tablets are supplied for oral administration in the following strengths and package configurations:

Table 11. CADUET Packaging Configurations

		CADUET		
Package Configuration	Tablet Strength (amlodipine besylate/ atorvastatin calcium) mg	NDC #	Engraving	Tablet Color
Bottle of 30	2.5/10	0069-2960-30	CDT 251	White
Bottle of 30	2.5/20	0069-2970-30	CDT 252	White
Bottle of 30	2.5/40	0069-2980-30	CDT 254	White
Bottle of 30	5/10	0069-2150-30	CDT 051	White
Bottle of 30	5/20	0069-2170-30	CDT 052	White
Bottle of 30	5/40	0069-2190-30	CDT 054	White
Bottle of 30	5/80	0069-2260-30	CDT 058	White
Bottle of 30	10/10	0069-2160-30	CDT 101	Blue
Bottle of 30	10/20	0069-2180-30	CDT 102	Blue
Bottle of 30	10/40	0069-2250-30	CDT 104	Blue
Bottle of 30	10/80	0069-2270-30	CDT 108	Blue

Store at 25 deg. C (77 deg. F); excursions permitted to 15-30 deg. C (59-86 deg. F) see USP Controlled Room Temperature .

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Dublin, Ireland

Distributed by

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LAB-0276-3.0 Revised October 2004

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GOODS AND/OR SERVICES

International Class: 005
Class Status: Active
PHARMACEUTICAL PREPARATIONS FOR THE TREATMENT OF CENTRAL NERVOUS SYSTEM DISEASES AND DISORDERS, NEUROLOGICAL DISORDERS, PAIN, EPILEPSY, MOOD DISORDERS, ANXIETY
Basis: 1(a)
First Use Date: 2004-11-12
First Use in Commerce Date: 2004-11-12

ADDITIONAL INFORMATION

(NOT AVAILABLE)

MADRID PROTOCOL INFORMATION

(NOT AVAILABLE)

PROSECUTION HISTORY

2005-12-13 - Registered - Principal Register

2005-10-25 - Law Office Registration Review Completed

2005-10-14 - Assigned To LIE

2005-10-11 - Allowed for Registration - Principal Register (SOU accepted)

2005-08-29 - Statement of use processing complete

2005-08-19 - Amendment to Use filed

2005-08-19 - TEAS Statement of Use Received

2005-08-09 - Notice of allowance - mailed

2005-05-17 - Published for opposition

2005-04-27 - Notice of publication

2005-02-01 - Law Office Publication Review Completed

2004-11-22 - Assigned To LIE

2004-11-16 - Approved for Pub - Principal Register (Initial exam)

2004-11-16 - Teas/Email Correspondence Entered

2004-11-15 - Communication received from applicant

2004-11-15 - TEAS Response to Office Action Received

2004-06-21 - Non-final action mailed

2004-06-18 - Assigned To Examiner

2004-02-03 - New Application Entered In Tram

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90 of 192 DOCUMENTS

Physician's Desk Reference for Prescription Drugs

Lyrica Capsules(Pfizer)

BODY:

DESCRIPTION

Pregabalin is described chemically as (*S*)-3-(aminomethyl)-5-methylhexanoic acid. The molecular formula is C[8] H[17] NO[2] and the molecular weight is 159.23. The chemical structure of pregabalin is:

See Image

Pregabalin is a white to off-white, crystalline solid with a pK[a1] of 4.2 and a pK[a2] of 10.6. It is freely soluble in water and both basic and acidic aqueous solutions. The log of the partition coefficient (n-octanol/0.05M phosphate buffer) at pH 7.4 is-1.35.

LYRICA (pregabalin) Capsules are supplied as imprinted hard-shell capsules containing 25, 50, 75, 100, 150, 200, 225, and 300 mg of pregabalin, along with lactose monohydrate, cornstarch, and talc as inactive ingredients. The capsule shells contain gelatin and titanium dioxide. In addition, the orange capsule shells contain red iron oxide and the white capsule shells contain sodium lauryl sulfate and colloidal silicon dioxide. Colloidal silicon dioxide is a manufacturing aid that may or may not be present in the capsule shells. The imprinting ink contains shellac, black iron oxide, propylene glycol, and potassium hydroxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

LYRICA (pregabalin) binds with high affinity to the alpha[2]-delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues. Although the mechanism of action of pregabalin is unknown, results with genetically modified mice and with compounds structurally related to pregabalin (such as gabapentin) suggest that binding to the alpha[2]-delta subunit may be involved in pregabalin's antinociceptive and antiseizure effects in animal models. *In vitro* , pregabalin reduces the calcium-dependent release of several neurotransmitters, possibly by modulation of calcium channel function.

While pregabalin is a structural derivative of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), it does not bind directly to GABA[A] , GABA[B] , or benzodiazepine receptors, does not augment GABA[A] responses in cultured neurons, does not alter rat brain GABA concentration or have acute effects on GABA uptake or degradation. However, in cultured neurons prolonged application of pregabalin increases the density of GABA transporter protein and increases the rate of functional GABA transport. Pregabalin does not block sodium channels, is not active at opiate receptors, and does not alter cyclooxygenase enzyme activity. It is inactive at serotonin and dopamine receptors and does not inhibit dopamine, serotonin, or noradrenaline reuptake.

Pharmacokinetics

Pregabalin is well absorbed after oral administration, is eliminated largely by renal excretion, and has an elimination half-life of about 6 hours.

Absorption and Distribution

Following oral administration of pregabalin capsules under fasting conditions, peak plasma concentrations occur within 1.5 hours. Pregabalin oral bioavailability is >/=90% and is independent of dose. Following single-(25 to 300 mg) and multiple-dose (75 to 900 mg/day) administration, maximum plasma concentrations (C[max]) and area under the plasma concentration-time curve (AUC) values increase linearly. Following repeated administration, steady state is achieved within 24 to 48 hours. Multiple-dose pharmacokinetics can be predicted from single-dose data.

The rate of pregabalin absorption is decreased when given with food, resulting in a decrease in C[max] of approximately 25% to 30% and an increase in T[max] to approximately 3 hours. However, administration of pregabalin with food has no clinically relevant effect on the total absorption of pregabalin. Therefore, pregabalin can be taken with or without food.

Pregabalin does not bind to plasma proteins. The apparent volume of distribution of pregabalin following oral administration is approximately 0.5 L/kg. Pregabalin is a substrate for system L transporter which is responsible for the transport of large amino acids across the blood brain barrier. Although there are no data in humans, pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys. In addition, pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats.

Metabolism and Elimination

Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabeled pregabalin, approximately 90% of the administered dose was recovered in the urine as unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, pregabalin (S-enantiomer) did not undergo racemization to the R-enantiomer in mice, rats, rabbits, or monkeys.

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug with a mean elimination half-life of 6.3 hours in subjects with normal renal function. Mean renal clearance was estimated to be 67.0 to 80.9 mL/min in young healthy subjects. Because pregabalin is not bound to plasma proteins this clearance rate indicates that renal tubular reabsorption is involved. Pregabalin elimination is nearly proportional to creatinine clearance (CLcr) (see Special Populations , Renal Impairment and DOSAGE AND ADMINISTRATION , Patients with Impaired Renal Function).

Special Populations

Race: In population pharmacokinetic analyses of the clinical studies in various populations, the pharmacokinetics of pregabalin were not significantly affected by race (Caucasians, Blacks, and Hispanics).

Gender: Population pharmacokinetic analyses of the clinical studies showed that the relationship between daily dose and pregabalin drug exposure is similar between genders.

Renal Impairment and Hemodialysis: Pregabalin clearance is nearly proportional to creatinine clearance (CLcr). Dosage reduction in patients with renal dysfunction is necessary. Pregabalin is effectively removed from plasma by hemodialysis. Following a 4-hour hemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%. For patients on hemodialysis, dosing must be modified (see DOSAGE AND ADMINISTRATION , Patients with Renal Impairment).

Elderly: Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in CLcr. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function (see DOSAGE AND ADMINISTRATION , Patients with Renal Impairment).

Pediatric Pharmacokinetics: Pharmacokinetics of pregabalin have not been adequately studied in pediatric patients.

Drug Interactions:

In Vitro Studies: Pregabalin, at concentrations that were, in general, 10-times those attained in clinical trials, does not inhibit human CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 enzyme systems. The potential of pregabalin to induce these enzymes has not been studied *in vitro* .

In Vivo Studies: The drug interaction studies described in this section were conducted in healthy adults, and across various patient populations.

Gabapentin: The pharmacokinetic interactions of pregabalin and gabapentin were investigated in 12 healthy subjects following concomitant single-dose administration of 100-mg pregabalin and 300-mg gabapentin and in 18 healthy subjects following concomitant multiple-dose administration of 200-mg pregabalin every 8 hours and 400-mg gabapentin every 8 hours. Gabapentin pharmacokinetics following single-and multiple-dose administration were unaltered by pregabalin coadministration. The extent of pregabalin absorption was unaffected by gabapentin coadministration, although there was a small reduction in rate of absorption.

Oral Contraceptive: Pregabalin coadministration (200 mg three times a day) had no effect on the steady-state pharmacokinetics of norethindrone and ethinyl estradiol (1 mg/35 micro g, respectively) in healthy subjects.

Lorazepam: Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of lorazepam single-dose pharmacokinetics and single-dose administration of lorazepam (1 mg) had no effect on the steady-state pharmacokinetics of pregabalin.

Oxycodone: Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of oxycodone single-dose pharmacokinetics. Single-dose administration of oxycodone (10 mg) had no effect on the steady-state pharmacokinetics of pregabalin.

Ethanol: Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of ethanol single-dose pharmacokinetics and single-dose administration of ethanol (0.7 g/kg) had no effect on the steady-state pharmacokinetics of pregabalin.

Phenytoin, carbamazepine, valproic acid, and lamotrigine: Steady-state trough plasma concentrations of phenytoin, carbamazepine and carbamazepine 10,11 epoxide, valproic acid, and lamotrigine were not affected by concomitant pregabalin (200 mg three times a day) administration. Population pharmacokinetic analyses in patients treated with pregabalin and various concomitant medications suggest the following:

Therapeutic class	Specific concomitant drug studied
Concomitant drug has no effect on the pharmacokinetics of pregabalin	
Hypoglycemics	Glyburide, insulin, metformin,
Diuretics	Furosemide
Antiepileptic Drugs	Tiagabine
Concomitant drug has no effect on the pharmacokinetics of pregabalin and pregabalin has no effect on the pharmacokinetics of concomitant drug	
Antiepileptic Drugs	Carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate, valproic acid

CLINICAL STUDIES

Neuropathic pain associated with diabetic peripheral neuropathy

The efficacy of the maximum recommended dose of LYRICA for the management of neuropathic pain associated with diabetic peripheral neuropathy was established in three double-blind, placebo-controlled, multicenter studies that enrolled 729 patients with three times a day dosing, two of which studied the maximum recommended dose. Studies

DPN 1 and DPN 2 enrolled a total of 483 patients of which 89% completed the studies. Patients enrolled had Type 1 or 2 diabetes mellitus with a diagnosis of painful distal symmetrical sensorimotor polyneuropathy for 1 to 5 years. The patients had a minimum mean baseline pain score of >/=4 on an 11-point numerical pain rating scale ranging from 0 (no pain) to 10 (worst possible pain). The baseline mean pain scores across the two studies ranged from 6.1 to 6.7. Patients were permitted up to 4 grams of acetaminophen per day as needed for pain, in addition to pregabalin. Patients recorded their pain daily in a diary.

Study DPN 1: This 5-week study of 337 patients (240 pregabalin and 97 placebo) compared LYRICA 25, 100, or 200 mg three times a day with placebo. Treatment with LYRICA 100 and 200 mg three times a day statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. There was no evidence of a greater effect on pain scores of the 200 mg three times a day dose than the 100 mg three times a day dose, but there was evidence of dose dependent adverse effects (see ADVERSE REACTIONS). For various degrees of improvement in pain from baseline to study endpoint, Figure 1 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

See Image

Study DPN 2: This 8-week study of 146 patients (76 pregabalin and 70 placebo) compared LYRICA 100 mg three times a day with placebo. Treatment with LYRICA 100 mg three times a day statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. For various degrees of improvement in pain from baseline to study endpoint, Figure 2 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

See Image

Postherpetic Neuralgia

The efficacy of LYRICA for the management of postherpetic neuralgia was established in three double-blind, placebo-controlled, multicenter studies. These studies enrolled 779 patients, of whom 566 completed the studies. These patients had neuralgia persisting for at least 3 months following healing of herpes zoster rash and a minimum baseline score of >/=4 on an 11-point numerical pain rating scale ranging from 0 (no pain) to 10 (worst possible pain). The baseline mean pain scores across the 3 studies ranged from 6 to 7. Patients were permitted up to 4 grams of acetaminophen per day as needed for pain, in addition to pregabalin. Patients recorded their pain daily in a diary.

Study PHN 1: This 13-week study of 368 patients (275 pregabalin and 93 placebo) compared LYRICA 75, 150, and 300 mg twice daily with placebo. Patients with creatinine clearance (CLcr) between 30 to 60 mL/min were randomized to 75 mg, 150 mg, or placebo twice daily. Patients with creatinine clearance greater than 60 mL/min were randomized to 75 mg, 150 mg, 300 mg or placebo twice daily. In patients with creatinine clearance greater than 60 mL/min treatment with all doses of LYRICA statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. Despite differences in dosing based on renal function, patients with creatinine clearance between 30 to 60 mL/min tolerated LYRICA less well than patients with creatinine clearance greater than 60 mL/min as evidenced by higher rates of discontinuation due to adverse events. For various degrees of improvement in pain from baseline to study endpoint, Figure 3 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

See Image

Study PHN 2: This 8-week study of 173 patients (89 pregabalin and 84 placebo) compared LYRICA 100 or 200 mg three times a day with placebo, with doses assigned based on creatinine clearance. Patients with creatinine clearance between 30 to 60 mL/min were treated with 100 mg three times a day, and patients with creatinine clearance greater than 60 mL/min were treated with 200 mg three times daily. Treatment with LYRICA statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. For various degrees of improvement in pain from baseline to study endpoint, Figure 4 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

See Image

Study PHN 3: This 8-week study of 238 patients (157 pregabalin and 81 placebo) compared LYRICA 50 or 100 mg three times a day with placebo with doses assigned regardless of creatinine clearance. Treatment with LYRICA 50 and 100 mg three times a day statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. Patients with creatinine clearance between 30 to 60 mL/min tolerated LYRICA less well than patients with creatinine clearance greater than 60 mL/min as evidenced by markedly higher rates of discontinuation due to adverse events. For various degrees of improvement in pain from baseline to study endpoint, Figure 5 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

See Image

Epilepsy

The efficacy of LYRICA as adjunctive therapy in partial onset seizures was established in three 12-week, randomized, double-blind, placebo-controlled, multicenter studies in 1052 adult patients. Patients were enrolled who had partial onset seizures with or without secondary generalization and were not adequately controlled with 1 to 3 concomitant antiepileptic drugs (AEDs). Patients taking gabapentin were required to discontinue gabapentin treatment 1 week prior to entering baseline. During an 8-week baseline period, patients had to experience at least 6 partial onset seizures with no seizure-free period exceeding 4 weeks. The mean duration of epilepsy was 25 years in these 3 studies and the mean and median baseline seizure frequencies were 22.5 and 10 seizures per month, respectively. Approximately half of the patients were taking 2 concurrent AEDs at baseline. Among the LYRICA-treated patients, 80% completed the double-blind phase of the studies.

Table 1 shows median baseline seizure rates and median percent reduction in seizure frequency by dose.

Table 1: Seizure Response in Controlled, Add-On Epilepsy Studies

Daily Dose of Pregabalin	Dosing Regimen	N	Baseline Seizure Frequency/mo	Median % Change from Baseline	p-value, vs. placebo
Study E1					
Placebo	BID	100	9.5	0	
50 mg/day	BID	88	10.3	-9	0.4230
150 mg/day	BID	86	8.8	-35	0.0001

300 mg/day	BID	90	9.8	-37	0.0001
600 mg/day	BID	89	9.0	-51	0.0001
Study E2					
Placebo	TID	96	9.3	1	
150 mg/day	TID	99	11.5	-17	0.0007
600 mg/day	TID	92	12.3	-43	0.0001
Study E3					
Placebo	BID/TID	98	11	-1	
600 mg/day	BID	103	9.5	-36	0.0001
600 mg/day	TID	111	10	-48	0.0001

In the first study (E1), there was evidence of a dose-response relationship for total daily doses of Lyrica between 150 and 600 mg/day; a dose of 50 mg/day was not effective. In the first study (E1), each daily dose was divided into two equal doses (twice a day dosing). In the second study (E2), each daily dose was divided into three equal doses (three times a day dosing). In the third study (E3), the same total daily dose was divided into two equal doses for one group (twice a day dosing) and three equal doses for another group (three times a day dosing). While the three times a day dosing group in Study E3 performed numerically better than the twice a day dosing group, this difference was small and not statistically significant.

A secondary outcome measure included the responder rate (proportion of patients with >/=50% reduction from baseline in partial seizure frequency). The following figure displays responder rate by dose for two of the studies.

See Image

See Image

Subset evaluations of the antiseizure efficacy of LYRICA showed no clinically important differences as a function of age, gender, or race.

INDICATIONS AND USAGE

LYRICA is indicated for management of

Neuropathic pain associated with diabetic peripheral neuropathyPostherpetic neuralgia

LYRICA is indicated as adjunctive therapy for adult patients with partial onset seizures.

CONTRAINDICATIONS

LYRICA is contraindicated in patients with known hypersensitivity to pregabalin or any of its components.

WARNINGS

Withdrawal of Antiepileptic Drugs (AEDs)

As with all AEDs, pregabalin should be withdrawn gradually to minimize the potential of increased seizure frequency in patients with seizure disorders. If pregabalin is discontinued this should be done gradually over a minimum of 1 week.

Tumorigenic Potential

In standard preclinical *in vivo* lifetime carcinogenicity studies of pregabalin, an unexpectedly high incidence of hemangiosarcoma was identified in two different strains of mice (see PRECAUTIONS : Carcinogenesis, Mutagenesis, Impairment of Fertility). The clinical significance of this finding is unknown. Clinical experience during pregabalin's

premarketing development provides no direct means to assess its potential for inducing tumors in humans.

In clinical studies across various patient populations, comprising 6396 patient-years of exposure in patients >12 years of age, new or worsening-preexisting tumors were reported in 57 patients. Without knowledge of the background incidence and recurrence in similar populations not treated with LYRICA, it is impossible to know whether the incidence seen in these cohorts is or is not affected by treatment.

PRECAUTIONS

Dizziness and Somnolence

Pregabalin causes dizziness and somnolence. Patients should be informed that pregabalin-related dizziness and somnolence may impair their ability to perform tasks such as driving or operating machinery (see PRECAUTIONS - Information for Patients).

In the pregabalin controlled trials, dizziness was experienced by 29% of pregabalin-treated patients compared to 9% of placebo-treated patients; somnolence was experienced by 22% of pregabalin-treated patients compared to 8% of placebo-treated patients. Dizziness and somnolence generally began shortly after the initiation of pregabalin therapy and occurred more frequently at higher doses. Dizziness and somnolence were the adverse events most frequently leading to withdrawal (4% each) from controlled studies. In pregabalin-treated patients reporting these adverse events in short-term, controlled studies, dizziness persisted until the last dose in 31% and somnolence persisted until the last dose in 46% of patients.

Ophthalmological Effects

In controlled studies, a higher proportion of patients treated with pregabalin reported blurred vision (6%) than did patients treated with placebo (2%), which resolved in a majority of cases with continued dosing. Less than 1% of patients discontinued pregabalin treatment due to vision-related events (primarily blurred vision).

Prospectively planned ophthalmologic testing, including visual acuity testing, formal visual field testing and dilated funduscopic examination, was performed in over 3600 patients. In these patients, visual acuity was reduced in 7% of patients treated with pregabalin, and 5% of placebo-treated patients. Visual field changes were detected in 13% of pregabalin-treated, and 12% of placebo-treated patients. Funduscopic changes were observed in 2% of pregabalin-treated and 2% of placebo-treated patients.

Although the clinical significance of the ophthalmologic findings is unknown, patients should be informed that if changes in vision occur, they should notify their physician. If visual disturbance persists, further assessment should be considered. More frequent assessment should be considered for patients who are already routinely monitored for ocular conditions (See PRECAUTIONS - Information for Patients).

Abrupt or Rapid Discontinuation

Following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache, and diarrhea. Pregabalin should be tapered gradually over a minimum of 1 week rather than discontinued abruptly.

Weight Gain

Pregabalin treatment caused weight gain. In pregabalin controlled clinical trials of up to 13 weeks, a gain of 7% or more over baseline weight was observed in 8% of pregabalin-treated patients and 2% of placebo-treated patients. Few patients treated with pregabalin (0.2%) withdrew from controlled trials due to weight gain. Pregabalin associated weight gain was related to dose and duration of exposure, but did not appear to be associated with baseline BMI, gender, or age. Weight gain was not limited to patients with edema (see PRECAUTIONS - Peripheral Edema).

Although weight gain was not associated with clinically important changes in blood pressure in short-term controlled studies, the long-term cardiovascular effects of pregabalin-associated weight gain are unknown.

Among diabetic patients, pregabalin-treated patients gained an average of 1.6 kg (range:-16 to 16 kg), compared to an average 0.3 kg (range:-10 to 9 kg) weight gain in placebo patients. In a cohort of 333 diabetic patients who received pregabalin for at least 2 years, the average weight gain was 5.2 kg.

While the effects of pregabalin-associated weight gain on glycemic control have not been systematically assessed, in controlled and longer-term open label clinical trials with diabetic patients, pregabalin treatment did not appear to be associated with loss of glycemic control (as measured by HbA[1C]).

Peripheral Edema

Pregabalin treatment caused edema, primarily described as peripheral edema. In short-term trials of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral edema and cardiovascular complications such as hypertension or congestive heart failure. Peripheral edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.

In controlled clinical trials the incidence of peripheral edema was 6% in the pregabalin group compared with 2% in the placebo group. In controlled clinical trials, 0.6% of pregabalin patients and no placebo patients withdrew due to peripheral edema.

Higher frequencies of weight gain and peripheral edema were observed in patients taking both LYRICA and a thiazolidinedione antidiabetic agent compared to patients taking either drug alone. The majority of patients using thiazolidinedione antidiabetic agents in the overall safety database were participants in studies of pain associated with diabetic peripheral neuropathy. In this population, peripheral edema was reported in 3% (2/60) of patients who were using thiazolidinedione antidiabetic agents only, 8% (69/859) of patients who were treated with pregabalin only, and 19% (23/120) of patients who were on both pregabalin and thiazolidinedione antidiabetic agents. Similarly, weight gain was reported in 0% (0/60) of patients on thiazolidinediones only; 4% (35/859) of patients on pregabalin only; and 7.5% (9/120) of patients on both drugs.

As the thiazolidinedione class of antidiabetic drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, care should be taken when co-administering LYRICA and these agents.

Because there are limited data on congestive heart failure patients with New York Heart Association (NYHA) Class III or IV cardiac status, LYRICA should be used with caution in these patients.

Creatine Kinase Elevations

Pregabalin treatment was associated with creatine kinase elevations. Mean changes in creatine kinase from baseline to the maximum value were 60 U/L for pregabalin-treated patients and 28 U/L for the placebo patients. In all controlled trials across multiple patient populations, 2% of patients on pregabalin and 1% of placebo patients had a value of creatine kinase at least three times the upper limit of normal. Three pregabalin treated subjects had events reported as rhabdomyolysis in premarketing clinical trials. The relationship between these myopathy events and pregabalin is not completely understood because the cases had documented factors that may have caused or contributed to these events. Prescribers should instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if these muscle symptoms are accompanied by malaise or fever. Pregabalin treatment should be discontinued if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.

Laboratory Changes

Decreased Platelet Count

Pregabalin treatment was associated with a decrease in platelet count. Pregabalin-treated subjects experienced a mean

maximal decrease in platelet count of 20 x 10[3] / micro L, compared to 11 x 10[3] / micro L in placebo patients. In the overall database of controlled trials, 2% of placebo patients and 3% of pregabalin patients experienced a potentially clinically significant decrease in platelets, defined as 20% below baseline value and <150 x 10[3] / micro L. In randomized controlled trials, pregabalin was not associated with an increase in bleeding related adverse events.

ECG Changes

PR Interval Prolongation

Pregabalin treatment was associated with mild PR interval prolongation. In analyses of clinical trial ECG data, the mean PR interval increase was 3-6 msec at pregabalin doses >/=300 mg/day. This mean change difference was not associated with an increased risk of PR increase >/=25% from baseline, an increased percentage of subjects with on-treatment PR >200 msec, or an increased risk of adverse events of second or third degree AV block.

Subgroup analyses did not identify an increased risk of PR prolongation in patients with baseline PR prolongation or in patients taking other PR prolonging medications. However, these analyses cannot be considered definitive because of the limited number of patients in these categories.

Information for Patients

Patients should be counseled that LYRICA may cause dizziness, somnolence, blurred vision and other CNS signs and symptoms. Accordingly, they should be advised not to drive, operate complex machinery, or engage in other hazardous activities until they have gained sufficient experience on pregabalin to gauge whether or not it affects their mental, visual, and/or motor performance adversely.

Patients should be counseled that LYRICA may cause visual disturbances. Patients should be informed that if changes in vision occur, they should notify their physician (see PRECAUTIONS).

Patients should be advised to take LYRICA as prescribed. Abrupt or rapid discontinuation may result in insomnia, nausea, headache, or diarrhea.

Patients should be counseled that LYRICA may cause edema and weight gain.

Patients should be advised that concomitant treatment with LYRICA and a thiazolidinedione antidiabetic agent may lead to an additive effect on edema and weight gain. For patients with preexisting cardiac conditions, this may increase the risk of heart failure.

Patients should be instructed to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Patients who require concomitant treatment with central nervous system depressants such as opiates or benzodiazepines should be informed that they may experience additive CNS side effects, such as somnolence.

Patients should be told to avoid consuming alcohol while taking LYRICA, as LYRICA may potentiate the impairment of motor skills and sedation of alcohol.

Patients should be instructed to notify their physician if they become pregnant or intend to become pregnant during therapy, and to notify their physician if they are breast feeding or intend to breast feed during therapy.

Men being treated with LYRICA who plan to father a child should be informed of the potential risk of male-mediated teratogenicity. In preclinical studies in rats, pregabalin was associated with an increased risk of male-mediated teratogenicity. The clinical significance of this finding is uncertain (see PRECAUTIONS , Carcinogenesis and Impairment of Fertility).

Diabetic patients should be instructed to pay particular attention to skin integrity while being treated with LYRICA. Some animals treated with pregabalin developed skin ulcerations, although no increased incidence of skin lesions associated with LYRICA was observed in clinical trials (see Animal Toxicology).

Patients should be informed of the availability of a patient information leaflet, and they should be instructed to read the leaflet prior to taking LYRICA.

Drug Interactions

Since pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), and does not bind to plasma proteins, its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions or protein binding displacement. *In vitro* and *in vivo* studies showed that LYRICA is unlikely to be involved in significant pharmacokinetic drug interactions. Specifically, there are no pharmacokinetic interactions between pregabalin and the following antiepileptic drugs: carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topiramate. Important pharmacokinetic interactions would also not be expected to occur between pregabalin and commonly used antiepileptic drugs (see CLINICAL PHARMACOLOGY).

Pharmacodynamics

Multiple oral doses of pregabalin were co-administered with oxycodone, lorazepam, or ethanol. Although no pharmacokinetic interactions were seen, additive effects on cognitive and gross motor functioning were seen when pregabalin was co-administered with those drugs. No clinically important effects on respiration were seen (see PRECAUTIONS , Dizziness and Somnolence and Information for Patients).

Animal Toxicology

Dermatopathy

Skin lesions ranging from erythema to necrosis were seen in repeated-dose toxicology studies in both rats and monkeys. The etiology of these skin lesions is unknown. At the maximum recommended human dose (MRD) of 600 mg/day, there is a 2-fold safety margin for the dermatological lesions. The more severe dermatopathies involving necrosis were associated with pregabalin exposures (as expressed by plasma AUCs) of approximately 3 to 8 times those achieved in humans given the MRD. No increase in incidence of skin lesions was observed in clinical studies.

Ocular Lesions

Ocular lesions (characterized by retinal atrophy including loss of photoreceptor cells and/or corneal inflammation/mineralization) were observed in two lifetime carcinogenicity studies in Wistar rats. These findings were observed at plasma pregabalin exposures (AUC) >/=2 times those achieved in humans given the maximum recommended dose of 600 mg/day. A no-effect dose for ocular lesions was not established. Similar lesions were not observed in lifetime carcinogenicity studies in two strains of mice or in monkeys treated for 1 year.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

A dose-dependent increase in the incidence of malignant vascular tumors (hemangiosarcomas) was observed in two strains of mice (B6C3F1 and CD-1) given pregabalin (200, 1000, or 5000 mg/kg) in the diet for two years. Plasma pregabalin exposure (AUC) in mice receiving the lowest dose that increased hemangiosarcomas was approximately equal to the human exposure at the maximum recommended dose (MRD) of 600 mg/day. A no-effect dose for induction of hemangiosarcomas in mice was not established. No evidence of carcinogenicity was seen in two studies in Wistar rats following dietary administration of pregabalin for two years at doses (50, 150, or 450 mg/kg in males and 100, 300, or 900 mg/kg in females) that were associated with plasma exposures in males and females up to approximately

14 and 24 times, respectively, human exposure at the MRD.

Mutagenesis

Pregabalin was not mutagenic in bacteria or in mammalian cells *in vitro* , was not clastogenic in mammalian systems *in vitro* and *in vivo* , and did not induce unscheduled DNA synthesis in mouse or rat hepatocytes.

Impairment of Fertility

In fertility studies in which male rats were orally administered pregabalin (50 to 2500 mg/kg) prior to and during mating with untreated females, a number of adverse reproductive and developmental effects were observed. These included decreased sperm counts and sperm motility, increased sperm abnormalities, reduced fertility, increased preimplantation embryo loss, decreased litter size, decreased fetal body weights, and an increased incidence of fetal abnormalities. Effects on sperm and fertility parameters were reversible in studies of this duration (3–4 months). The no-effect dose for male reproductive toxicity in these studies (100 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately 3 times human exposure at the maximum recommended dose (MRD) of 600 mg/day.

In addition, adverse effects on reproductive organ (testes, epididymides) histopathology were observed in male rats exposed to pregabalin (500 to 1250 mg/kg) in general toxicology studies of four weeks or greater duration. The no-effect dose for male reproductive organ histopathology in rats (250 mg/kg) was associated with a plasma exposure approximately 8 times human exposure at the MRD.

In a fertility study in which female rats were given pregabalin (500, 1250, or 2500 mg/kg) orally prior to and during mating and early gestation, disrupted estrous cyclicity and an increased number of days to mating were seen at all doses, and embryolethality occurred at the highest dose. The low dose in this study produced a plasma exposure approximately 9 times that in humans receiving the MRD. A no-effect dose for female reproductive toxicity in rats was not established.

Human Data

In a double-blind, placebo-controlled clinical trial to assess the effect of pregabalin on sperm motility, 30 healthy male subjects were exposed to pregabalin at a dose of 600 mg/day. After 3 months of treatment (one complete sperm cycle), the difference between placebo-and pregabalin-treated subjects in mean percent sperm with normal motility was $<4\%$ and neither group had a mean change from baseline of more than 2%. Effects on other male reproductive parameters in humans have not been adequately studied.

Pregnancy

Pregnancy Category C

Increased incidences of fetal structural abnormalities and other manifestations of developmental toxicity, including lethality, growth retardation, and nervous and reproductive system functional impairment, were observed in the offspring of rats and rabbits given pregabalin during pregnancy, at doses that produced plasma pregabalin exposures (AUC) $>/=5$ times human exposure at the maximum recommended dose (MRD) of 600 mg/day.

When pregnant rats were given pregabalin (500, 1250, or 2500 mg/kg) orally throughout the period of organogenesis, incidences of specific skull alterations attributed to abnormally advanced ossification (premature fusion of the jugal and nasal sutures) were increased at $>/=1250$ mg/kg, and incidences of skeletal variations and retarded ossification were increased at all doses. Fetal body weights were decreased at the highest dose. The low dose in this study was associated with a plasma exposure (AUC) approximately 17 times human exposure at the MRD of 600 mg/day. A no-effect dose for rat embryo-fetal developmental toxicity was not established.

When pregnant rabbits were given pregabalin (250, 500, or 1250 mg/kg) orally throughout the period of organogenesis, decreased fetal body weight and increased incidences of skeletal malformations, visceral variations, and retarded

ossification were observed at the highest dose. The no-effect dose for developmental toxicity in rabbits (500 mg/kg) was associated with a plasma exposure approximately 16 times human exposure at the MRD.

In a study in which female rats were dosed with pregabalin (50, 100, 250, 1250, or 2500 mg/kg) throughout gestation and lactation, offspring growth was reduced at >/= 100 mg/kg and offspring survival was decreased at >/= 250 mg/kg. The effect on offspring survival was pronounced at doses >/=1250 mg/kg, with 100% mortality in high-dose litters. When offspring were tested as adults, neurobehavioral abnormalities (decreased auditory startle responding) were observed at >/=250 mg/kg and reproductive impairment (decreased fertility and litter size) was seen at 1250 mg/kg. The no-effect dose for pre-and postnatal developmental toxicity in rats (50 mg/kg) produced a plasma exposure approximately 2 times human exposure at the MRD.

There are no adequate and well-controlled studies in pregnant women. LYRICA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The effects of pregabalin on labor and delivery in pregnant women are unknown. In the prenatal-postnatal study in rats, pregabalin prolonged gestation and induced dystocia at exposures >/=50 times the mean human exposure (AUC[(0-24)] of 123 micro g*hr/mL) at the maximum recommended clinical dose of 600 mg/day.

Use in Nursing Mothers: It is not known if pregabalin is excreted in human milk; it is, however, present in the milk of rats. Because many drugs are excreted in human milk, and because of the potential for tumorigenicity shown for pregabalin in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and efficacy of pregabalin in pediatric patients have not been established.

In studies in which pregabalin (50 to 500 mg/kg) was orally administered to young rats from early in the postnatal period (Postnatal Day 7) through sexual maturity, neurobehavioral abnormalities (deficits in learning and memory, altered locomotor activity, decreased auditory startle responding and habituation) and reproductive impairment (delayed sexual maturation and decreased fertility in males and females) were observed at doses >/=50 mg/kg. The neurobehavioral changes persisted in animals tested after cessation of dosing and, thus, were considered to represent long-term effects. The low effect dose for developmental neurotoxicity and reproductive impairment in juvenile rats (50 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately equal to human exposure at the maximum recommended dose of 600 mg/day. A no-effect dose was not established.

Geriatric Use

In controlled clinical studies of LYRICA in neuropathic pain associated with diabetic peripheral neuropathy, 306 patients were 65 to 74 years of age, and 88 patients were 75 years of age or older.

In controlled clinical studies of LYRICA in neuropathic pain associated with postherpetic neuralgia, 282 patients were 65 to 74 years of age, and 379 patients were 75 years of age or older.

In controlled clinical studies of LYRICA in epilepsy, there were only 10 patients 65 to 74 years of age, and 2 patients who were 75 years of age or older.

No overall differences in safety and efficacy were observed between these patients and younger patients. Even though the incidence of adverse events did not increase with age, greater sensitivity of some older individuals cannot be ruled out. LYRICA is known to be substantially excreted by the kidney, and the risk of toxic reactions to LYRICA may be greater in patients with impaired renal function.

Because LYRICA is eliminated primarily by renal excretion, the dose should be adjusted for elderly patients with renal impairment, as noted in the DOSAGE AND ADMINISTRATION section.

ADVERSE REACTIONS

In all controlled and uncontrolled trials across various patient populations during the premarketing development of pregabalin, more than 10,000 patients have received pregabalin. Approximately 5000 patients were treated for 6 months or more, over 3100 patients were treated for 1 year or longer, and over 1400 patients were treated for at least 2 years.

Adverse Events Most Commonly Leading to Discontinuation in All Controlled Clinical Studies

In controlled trials of all populations combined, 14% of patients treated with pregabalin and 7% of patients treated with placebo discontinued prematurely due to adverse events. In the pregabalin treatment group, the adverse events most frequently leading to discontinuation were dizziness (4%) and somnolence (3%). In the placebo group, 1% of patients withdrew due to dizziness and <1% withdrew due to somnolence. Other adverse events that led to discontinuation from controlled trials more frequently in the pregabalin group compared to the placebo group were ataxia, confusion, asthenia, thinking abnormal, blurred vision, incoordination, and peripheral edema (1% each).

Most Common Adverse Events in All Controlled Clinical Studies

In controlled trials of all patient populations combined, dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, and "thinking abnormal" (primarily difficulty with concentration/attention) were more commonly reported by subjects treated with pregabalin than by subjects treated with placebo (>/=5% and twice the rate of that seen in placebo).

Controlled Studies with Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

Adverse Events Leading to Discontinuation

In clinical trials in patients with neuropathic pain associated with diabetic peripheral neuropathy, 9% of patients treated with pregabalin and 4% of patients treated with placebo discontinued prematurely due to adverse events. In the pregabalin treatment group, the most common reasons for discontinuation due to adverse events were dizziness (3%) and somnolence (2%). In comparison, <1% of placebo patients withdrew due to dizziness and somnolence. Other reasons for discontinuation from the trials, occurring with greater frequency in the pregabalin group than in the placebo group, were asthenia, confusion, and peripheral edema. Each of these events led to withdrawal in approximately 1% of patients.

Most Common Adverse Events

Table 2 lists all adverse events, regardless of causality, occurring in >/=1% of patients with neuropathic pain associated with diabetic neuropathy in the combined pregabalin group for which the incidence was greater in this combined pregabalin group than in the placebo group. A majority of pregabalin-treated patients in clinical studies had adverse events with a maximum intensity of "mild" or "moderate".

Table 2. Treatment-emergent adverse event incidence in controlled trials in Neuropathic Pain Associated with Diabetic Peripheral Neuropathy (Events in at least 1% of all LYRICA-treated patients and at least numerically more in all pregabalin than in the placebo group)

Body system - Preferred term	75 mg/day N=77 %	150 mg/day N=212	300 mg/day N=321	600 mg/day N=369	All PGB * N=979	Placebo N=459 %

Table 2. Treatment-emergent adverse event incidence in controlled trials in Neuropathic Pain Associated with Diabetic Peripheral Neuropathy (Events in at least 1% of all LYRICA-treated patients and at least numerically more in all pregabalin than in the placebo group)

		%	%	%	%	
Body as a whole						
Asthenia	4	2	4	7	5	2
Accidental injury	5	2	2	6	4	3
Back pain	0	2	1	2	2	0
Chest pain	4	1	1	2	2	1
Face edema	0	1	1	2	1	0
Digestive system						
Dry mouth	3	2	5	7	5	1
Constipation	0	2	4	6	4	2
Flatulence	3	0	2	3	2	1
Metabolic and nutritional disorders						
Peripheral edema	4	6	9	12	9	2
Weight gain	0	4	4	6	4	0
Edema	0	2	4	2	2	0
Hypoglycemia	1	3	2	1	2	1
Nervous system						
Dizziness	8	9	23	29	21	5
Somnolence	4	6	13	16	12	3
Neuropathy	9	2	2	5	4	3
Ataxia	6	1	2	4	3	1
Vertigo	1	2	2	4	3	1
Confusion	0	1	2	3	2	1
Euphoria	0	0	3	2	2	0
Incoordination	1	0	2	2	2	0
Thinking abnormal [a]	1	0	1	3	2	0
Tremor	1	1	1	2	1	0
Abnormal gait	1	0	1	3	1	0
Amnesia	3	1	0	2	1	0
Nervousness	0	1	1	1	1	0
Respiratory system						
Dyspnea	3	0	2	2	2	1
Special senses						
Blurry vision[b]	3	1	3	6	4	2
Abnormal vision	1	0	1	1	1	0

*PGB: pregabalin

[a] Thinking abnormal primarily consists of events related to difficulty

Table 2. Treatment-emergent adverse event incidence in controlled trials in Neuropathic Pain Associated with Diabetic Peripheral Neuropathy (Events in at least 1% of all LYRICA-treated patients and at least numerically more in all pregabalin than in the placebo group)

with concentration/attention but also includes events related to cognition and language problems and slowed thinking.
[b] Investigator term; summary level term is amblyopia.

Controlled Studies in Postherpetic Neuralgia

Adverse Events Leading to Discontinuation

In clinical trials in patients with postherpetic neuralgia, 14% of patients treated with pregabalin and 7% of patients treated with placebo discontinued prematurely due to adverse events. In the pregabalin treatment group, the most common reasons for discontinuation due to adverse events were dizziness (4%) and somnolence (3%). In comparison, less than 1% of placebo patients withdrew due to dizziness and somnolence. Other reasons for discontinuation from the trials, occurring in greater frequency in the pregabalin group than in the placebo group, were confusion (2%), as well as peripheral edema, asthenia, ataxia, and abnormal gait (1% each).

Most Common Adverse Events

Table 2 lists all adverse events, regardless of causality, occurring in >/= 1% of patients with neuropathic pain associated with postherpetic neuralgia in the combined pregabalin group for which the incidence was greater in this combined pregabalin group than in the placebo group. In addition, an event is included, even if the incidence in the all pregabalin group is not greater than in the placebo group, if the incidence of the event in the 600 mg/day group is more than twice that in the placebo group. A majority of pregabalin-treated patients in clinical studies had adverse events with a maximum intensity of "mild" or "moderate".

Table 3. Treatment-emergent adverse event incidence in controlled trials in Neuropathic Pain Associated with Postherpetic Neuralgia (Events in at least 1% of all LYRICA-treated patients and at least numerically more in all pregabalin than in the placebo group)

Body system - Preferred term	75 mg/d N=84 %	150 mg/d N=302 %	300 mg/d N=312 %	600 mg/d N=154 %	All PGB * N=852 %	Placebo N=398 %
Body as a whole						
Infection	14	8	6	3	7	4
Headache	5	9	5	8	7	5
Pain	5	4	5	5	5	4
Accidental injury	4	3	3	5	3	2
Flu syndrome	1	2	2	1	2	1
Face edema	0	2	1	3	2	1
Digestive system						
Dry mouth	7	7	6	15	8	3
Constipation	4	5	5	5	5	2
Flatulence	2	1	2	3	2	1

Table 3. Treatment-emergent adverse event incidence in controlled trials in Neuropathic Pain Associated with Postherpetic Neuralgia (Events in at least 1% of all LYRICA-treated patients and at least numerically more in all pregabalin than in the placebo group)

Vomiting	1	1	3	3	2	1
Metabolic and nutritional disorders						
Peripheral edema	0	8	16	16	12	4
Weight gain	1	2	5	7	4	0
Edema	0	1	2	6	2	1
Musculoskeletal system						
Myasthenia	1	1	1	1	1	0
Nervous system						
Dizziness	11	18	31	37	26	9
Somnolence	8	12	18	25	16	5
Ataxia	1	2	5	9	5	1
Abnormal gait	0	2	4	8	4	1
Confusion	1	2	3	7	3	0
Thinking Abnormal [a]	0	2	1	6	2	2
Incoordination	2	2	1	3	2	0
Amnesia	0	1	1	4	2	0
Speech disorder	0	0	1	3	1	0
Respiratory system						
Bronchitis	0	1	1	3	1	1
Special senses						
Blurry vision[b]	1	5	5	9	5	3
Diplopia	0	2	2	4	2	0
Abnormal vision	0	1	2	5	2	0
Eye disorder	0	1	1	2	1	0
Urogenital System						
Urinary incontinence	0	1	1	2	1	0

*PGB: pregabalin
[a] Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.
[b] Investigator term; summary level term is amblyopia.

Controlled Add-On Studies in Epilepsy

Adverse Events Leading to Discontinuation

Approximately 15% of patients receiving pregabalin and 6% of patients receiving placebo in add-on epilepsy trials

discontinued prematurely due to adverse events. In the pregabalin treatment group, the adverse events most frequently leading to discontinuation were dizziness (6%), ataxia (4%), and somnolence (3%). In comparison, <1% of patients in the placebo group withdrew due to each of these events. Other adverse events that led to discontinuation of at least 1% of patients in the pregabalin group and at least twice as frequently compared to the placebo group were asthenia, diplopia, blurred vision, thinking abnormal, nausea, tremor, vertigo, headache, and confusion (which each led to withdrawal in 2% or less of patients).

Most Common Adverse Events

Table 4 lists all dose-related adverse events, regardless of causality, occurring in at least 2% of all LYRICA-treated patients. Dose-relatedness was defined as the incidence of the adverse event in the 600 mg/day group was at least 2% greater than the rate in both the placebo and 150 mg/day groups. In these studies, 758 patients received pregabalin and 294 patients received placebo for up to 12 weeks. Because patients were also treated with 1 to 3 other AEDs, it is not possible to determine whether the following adverse events can be ascribed to pregabalin alone, or the combination of pregabalin and other AEDs. A majority of pregabalin-treated patients in these studies had adverse events with a maximum intensity of "mild" or "moderate".

Table 4. Dose-related treatment-emergent adverse event incidence in controlled trials in Epilepsy (Events in at least 2% of all LYRICA-treated patients and the adverse event in the 600 mg/day group was >/=2% the rate in both the placebo and 150 mg/day groups)

Body System - Preferred Term	150 mg/d N=185 %	300 mg/d N=90 %	600 mg/d N=395 %	All PGB * N=670 [a] %	Placebo N=294 %
Body as a Whole					
Accidental Injury	7	11	10	9	5
Pain	3	2	5	4	3
Digestive System					
Increased Appetite	2	3	6	5	1
Dry Mouth	1	2	6	4	1
Constipation	1	1	7	4	2
Metabolic and Nutritional Disorders					
Weight Gain	5	7	16	12	1
Peripheral Edema	3	3	6	5	2
Nervous System					
Dizziness	18	31	38	32	11
Somnolence	11	18	28	22	11
Ataxia	6	10	20	15	4
Tremor	3	7	11	8	4
Thinking Abnormal[b]	4	8	9	8	2
Amnesia	3	2	6	5	2
Speech Disorder	1	2	7	5	1
Incoordination	1	3	6	4	1

Table 4. Dose-related treatment-emergent adverse event incidence in controlled trials in Epilepsy (Events in at least 2% of all LYRICA-treated patients and the adverse event in the 600 mg/day group was >/=2% the rate in both the placebo and 150 mg/day groups)

Abnomral Gait	1	3	5	4	0
Twitching	0	4	5	4	1
Confusion	1	2	5	4	2
Myoclonus	1	0	4	2	0
Special Senses					
Blurry Vision[c]	5	8	12	10	4
Diplopia	5	7	12	9	4
Abnormal Vision	3	1	5	4	1

*PGB: pregabalin
[a] Excludes patients who received the 50 mg dose in Study E1.
[b] Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.
[c] Investigator term; summary level term is amblyopia.

Adverse events occurring in >/= 2% of patients with partial onset seizures in the combined pregabalin group for which the incidence was greater in this combined pregabalin group than in the placebo group, but did not show dose-relatedness, include the following: asthenia, infection, chest pain, vomiting, nervousness, nystagmus, paresthesias, visual field defect.

Other Adverse Events Observed During the Clinical Studies of LYRICA (pregabalin)

Following is a list of treatment-emergent adverse events reported by patients treated with LYRICA during all clinical trials. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening.

Events are categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are described in the WARNINGS and PRECAUTIONS sections.

Body as a Whole - *Frequent:* Abdominal pain, Allergic reaction, Fever, *Infrequent:* Abscess, Cellulitis, Chills, Malaise, Neck rigidity, Overdose, Pelvic pain, Photosensitivity reaction, Suicide attempt, *Rare:* Anaphylactoid reaction, Ascites, Granuloma, Hangover effect, Intentional Injury, Retroperitoneal Fibrosis, Shock, Suicide

Cardiovascular System - *Infrequent:* Deep thrombophlebitis, Heart failure, Hypotension, Postural hypotension, Retinal vascular disorder, Syncope; *Rare:* ST Depressed, Ventricular Fibrillation

Digestive System - *Frequent:* Gastroenteritis, Increased appetite; *Infrequent:* Cholecystitis, Cholelithiasis, Colitis, Dysphagia, Esophagitis, Gastritis, Gastrointestinal hemorrhage, Melena, Mouth ulceration, Pancreatitis, Rectal hemorrhage, Tongue edema; *Rare:* Aphthous stomatitis, Esophageal Ulcer

Hemic and Lymphatic System - *Frequent:* Ecchymosis; *Infrequent:* Anemia, Eosinophilia, Hypochromic anemia, Leukocytosis, Leukopenia, Lymphadenopathy, Thrombocytopenia; *Rare:* Myelofibrosis, Polycythemia, Prothrombin decreased, Purpura, Thrombocythemia

Metabolic and Nutritional Disorders - *Rare:* Glucose Tolerance Decreased, Urate Crystalluria

Musculoskeletal System - *Frequent:* Arthralgia, Leg cramps, Myalgia, Myasthenia; *Infrequent:* Arthrosis; *Rare:* Generalized Spasm

Nervous System - *Frequent:* Anxiety, Depersonalization, Hypertonia, Hypesthesia, Libido decreased, Nystagmus, Paresthesia, Stupor, Twitching; *Infrequent:* Abnormal dreams, Agitation, Apathy, Aphasia, Circumoral paresthesia, Dysarthria, Hallucinations, Hostility, Hyperalgesia, Hyperesthesia, Hyperkinesia, Hypokinesia, Hypotonia, Libido increased, Myoclonus, Neuralgia, *Rare:* Addiction, Cerebellar syndrome, Cogwheel rigidity, Coma, Delirium, Delusions, Dysautonomia, Dyskinesia, Dystonia, Encephalopathy, Extrapyramidal syndrome, Guillain Barre syndrome, Hypalgesia, Intracranial hypertension, Manic reaction, Paranoid reaction, Peripheral neuritis, Psychotic depression, Schizophrenic reaction, Torticollis, Trismus

Respiratory System - *Rare:* Apnea, Atelectasis, Bronchiolitis, Hiccup, Laryngismus, Lung edema, Lung fibrosis, Yawn

Skin and Appendages - *Frequent:* Pruritus, *Infrequent:* Alopecia, Dry skin, Eczema, Hirsutism, Skin ulcer, Urticaria, Vesiculobullous rash; *Rare:* Angioedema, Exfoliative dermatitis, Lichenoid dermatitis, Melanosis, Petechial rash, Purpuric rash, Pustular rash, Skin atrophy, Skin necrosis, Skin nodule, Stevens-Johnson syndrome, Subcutaneous nodule

Special senses - *Frequent:* Conjunctivitis, Diplopia, Otitis media, Tinnitus; *Infrequent:* Abnormality of accommodation, Blepharitis, Dry eyes, Eye hemorrhage, Hyperacusis, Photophobia, Retinal edema, Taste loss, Taste perversion; *Rare:* Anisocoria, Blindness, Corneal ulcer, Exophthalmos, Extraocular palsy, Iritis, Keratitis, Keratoconjunctivitis, Miosis, Mydriasis, Night blindness, Ophthalmoplegia, Optic atrophy, Papilledema, Parosmia, Ptosis, Uveitis

Urogenital System - *Frequent:* Anorgasmia, Impotence, Urinary frequency, Urinary incontinence, *Infrequent:* Abnormal ejaculation, Albuminuria, Amenorrhea, Dysmenorrhea, Dysuria, Hematuria, Kidney calculus, Leukorrhea, Menorrhagia, Metrorrhagia, Nephritis, Oliguria, Urinary retention, *Rare:* Acute kidney failure, Balanitis, Bladder Neoplasm, Cervicitis, Dyspareunia, Epididymitis, Female lactation, Glomerulitis

Comparison of Gender and Race

The overall adverse event profile of pregabalin was similar between women and men. There are insufficient data to support a statement regarding the distribution of adverse experience reports by race.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: LYRICA is a Schedule V controlled substance.

In a study of recreational users (N=15) of sedative/hypnotic drugs, including alcohol, Lyrica (450 mg, single dose) received subjective ratings of "good drug effect," "high" and "liking" to a degree that was similar to diazepam (30 mg, single dose). In controlled clinical studies in over 5500 patients, 4% of Lyrica-treated patients and 1% of placebo-treated patients overall reported euphoria as an adverse event, though in some patient populations studied, this reporting rate was higher and ranged from 1 to 12%. In clinical studies, following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache or diarrhea (see PRECAUTIONS , Abrupt Discontinuation), suggestive of physical dependence.

Pregabalin is not known to be active at receptor sites associated with drugs of abuse. As with any CNS active drug, physicians should carefully evaluate patients for history of drug abuse and observe them for signs of LYRICA misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behavior).

OVERDOSAGE

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans

There is limited experience with overdose of pregabalin. The highest reported accidental overdose of pregabalin during the clinical development program was 8000 mg, and there were no notable clinical consequences. In clinical studies, some patients took as much as 2400 mg/day. The types of adverse events experienced by patients exposed to higher doses (>/=900 mg) were not clinically different from those of patients administered recommended doses of pregabalin.

Treatment or Management of Overdose

There is no specific antidote for overdose with pregabalin. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; usual precautions should be observed to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. A Certified Poison Control Center should be contacted for up-to-date information on the management of overdose with pregabalin.

Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment. Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours).

DOSAGE AND ADMINISTRATION

LYRICA(TM) is given orally with or without food.

Neuropathic pain associated with diabetic peripheral neuropathy

The maximum recommended dose of LYRICA is 100 mg three times a day (300 mg/day) in patients with creatinine clearance of at least 60 mL/min. Dosing should begin at 50 mg three times a day (150 mg/day) and may be increased to 300 mg/day within 1 week based on efficacy and tolerability. Because LYRICA is eliminated primarily by renal excretion, the dose should be adjusted for patients with reduced renal function (see Patients with Renal Impairment).

Although LYRICA was also studied at 600 mg/day, there is no evidence that this dose confers additional significant benefit and this dose was less well tolerated. In view of the dose-dependent adverse effects, treatment with doses above 300 mg/day are not recommended (see ADVERSE REACTIONS).

When discontinuing LYRICA, taper gradually over a minimum of 1 week.

Postherpetic neuralgia

The recommended dose of LYRICA is 75 to 150 mg two times a day, or 50 to 100 mg three times a day (150 to 300 mg/day) in patients with creatinine clearance of at least 60 mL/min. Dosing should begin at 75 mg two times a day, or 50 mg three times a day (150 mg/day) and may be increased to 300 mg/day within 1 week based on efficacy and tolerability. Because LYRICA is eliminated primarily by renal excretion, the dose should be adjusted for patients with reduced renal function (see Patients with Renal Impairment).

Patients who do not experience sufficient pain relief following 2 to 4 weeks of treatment with 300 mg/day, and who are able to tolerate LYRICA, may be treated with up to 300 mg two times a day, or 200 mg three times a day (600 mg/day). In view of the dose-dependent adverse effects and the higher rate of treatment discontinuation due to adverse events, dosing above 300 mg/day should be reserved only for those patients who have on-going pain and are tolerating 300 mg daily (see ADVERSE REACTIONS).

When discontinuing LYRICA, taper gradually over a minimum of 1 week.

Epilepsy

LYRICA at doses of 150 to 600 mg/day has been shown to be effective as adjunctive therapy in the treatment of partial onset seizures in adults. The total daily dose should be divided and given either two or three times daily. Both the efficacy and adverse event profiles of LYRICA have been shown to be dose-related. In general, it is recommended that patients be started on a total daily dose no greater than 150 mg/day (75 mg two times a day, or 50 mg three times a day). Based on individual patient response and tolerability, the dose may be increased to a maximum dose of 600 mg/day.

The effect of dose escalation rate on the tolerability of LYRICA has not been formally studied.

The efficacy of add-on LYRICA in patients taking gabapentin has not been evaluated in controlled trials. Consequently, dosing recommendations for the use of LYRICA with gabapentin cannot be offered.

When discontinuing LYRICA, taper gradually over a minimum of 1 week.

Patients with Renal Impairment:

In view of dose-dependent adverse events and since LYRICA is eliminated primarily by renal excretion, the dose should be adjusted in patients with reduced renal function. Dosage adjustment in patients with renal impairment should be based on CLcr, as indicated in Table 3. To use this dosing table, an estimate of the patient's CLcr in mL/min is needed. CLcr in mL/min may be estimated from serum creatinine (mg/dL) determination using the Cockcroft and Gault equation:

$$CL[Cr] = \frac{140 - \text{age (years)}}{72 \times \text{serum creatinine (mg/dL)}} \times \text{weight (kg)} \quad (\times 0.85 \text{ for female patients})$$

For patients undergoing hemodialysis, pregabalin daily dose should be adjusted based on renal function. In addition to the daily dose adjustment, a supplemental dose should be given immediately following every 4-hour hemodialysis treatment (see Table 3).

Table 5: Pregabalin Dosage Adjustment Based on Renal Function

Creatinine Clearance (CLcr)	Total Pregabalin Daily Dose(mg/day)[a]			Dose Regimen
(mL/min)				
>/=60	150	300	600	BID or TID
30-60	75	150	300	BID or TID
15-30	25-50	75	150	QD or BID
<15	25	25-50	75	QD
Supplementary dosage following hemodialysis (mg)[b]				
Patients on the 25 mg QD regimen: take one supplemental dose of 25 mg or 50 mg				
Patients on the 25-50 mg QD regimen: take one supplemental dose of 50 mg or 75 mg				
Patients on the 75 mg QD regimen: take one supplemental dose of 100 mg or 150 mg				

TID = Three divided doses; BID = Two divided doses; QD =

Table 5: Pregabalin Dosage Adjustment Based on Renal Function

Single daily dose.
[a] Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.
[b] Supplementary dose is a single additional dose.

HOW SUPPLIED

25-mg capsules:

White, hard-gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 25" on the body; available in:

Bottles of 90: NDC 0071-1012-68

50-mg capsules:

White, hard-gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 50" and an ink band on the body, available in:

Bottles of 90: NDC 0071-1013-68

75-mg capsules:

White/orange, hard-gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 75" on the body; available in:

Bottles of 90: NDC 0071-1014-68

100-mg capsules:

Orange, hard-gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 100" on the body, available in:

Bottles of 90: NDC 0071-1015-68

150-mg capsules:

White, hard-gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 150" on the body, available in:

Bottles of 90: NDC 0071-1016-68

200-mg capsules:

Light orange, hard-gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 200" on the body, available in:

Bottles of 90: NDC 0071-1017-68

225-mg capsules:

White/light orange, hard-gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 225" on the body; available in:

Bottles of 90: NDC 0071-1019-68

300-mg capsules:

White/orange, hard-gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 300" on the body, available in:

Bottles of 90: NDC 0071-1018-68

Storage

Store at 25 deg. C (77 deg. F); excursions permitted to 15 deg. C to 30 deg. C (59 deg. F to 86 deg. F) (see USP Controlled Room Temperature).

Rx Only

Pfizer

Distributed by:

Parke-Davis

Division of Pfizer Inc, NY, NY 10017

LAB-0294-3.0 July 2005

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See Image

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Serial Number: 73659611 Assignment Information

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Filing Date: 1987-05-08

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Register: Principal

Law Office Assigned: (NOT AVAILABLE)

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PFIZER INC.
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NEW YORK, NY 10017
United States
Legal Entity Type: Corporation
State or Country of Incorporation: Delaware

GOODS AND/OR SERVICES

International Class: 005
Class Status: Active

PHARMACEUTICAL PREPARATION HAVING ANTIANGINAL AND ANTIHYPERTENSIVE PROPERTIES
Basis: 1(a)
First Use Date: 1987-04-08
First Use in Commerce Date: 1987-04-08

ADDITIONAL INFORMATION

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MADRID PROTOCOL INFORMATION

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1987-12-15 - Registered - Principal Register

1987-09-22 - Published for opposition

1987-08-21 - Notice of publication

1987-08-03 - Approved for Pub - Principal Register (Initial exam)

1987-07-28 - Assigned To Examiner

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106 of 192 DOCUMENTS

Physician's Desk Reference for Prescription Drugs

Norvasc Tablets(Pfizer)

BODY:

DESCRIPTION

NORVASC[(R)] is the besylate salt of amlodipine, a long-acting calcium channel blocker.

Amlodipine besylate is chemically described as 3-Ethyl-5-methyl (+/-)-2-(2-aminoethoxy)methyl-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, mono-benzenesulphonate. Its empirical formula is C[20] H[25] ClN[2] O[5] *C[6] H[6] O[3] S, and its structural formula is:

See Image

Amlodipine besylate is a white crystalline powder with a molecular weight of 567.1. It is slightly soluble in water and sparingly soluble in ethanol. NORVASC (amlodipine besylate) tablets are formulated as white tablets equivalent to 2.5, 5 and 10 mg of amlodipine for oral administration. In addition to the active ingredient, amlodipine besylate, each tablet contains the following inactive ingredients: microcrystalline cellulose, dibasic calcium phosphate anhydrous, sodium starch glycolate, and magnesium stearate.

CLINICAL PHARMACOLOGY

Mechanism of Action

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected *in vitro* but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodidpine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

The precise mechanisms by which amlodipine relieves angina have not been fully delineated, but are thought to include the following:

Exertional Angina: In patients with exertional angina, NORVASC reduces the total peripheral resistance (afterload) against which the heart works and reduces the rate pressure product, and thus myocardial oxygen demand, at any given level of exercise.

Vasospastic Angina: NORVASC has been demonstrated to block constriction and restore blood flow in coronary arteries and arterioles in response to calcium, potassium epinephrine, serotonin, and thromboxane A[2] analog in experimental animal models and in human coronary vessels *in vitro* . This inhibition of coronary spasm is responsible for the

effectiveness of NORVASC in vasospastic (Prinzmetal's or variant) angina.

Pharmacokinetics and Metabolism: After oral administration of therapeutic doses of NORVASC, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 and 90%. The bioavailability of NORVASC is not altered by the presence of food.

Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine. *Ex vivo* studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients. Elimination from the plasma is biphasic with a terminal elimination half-life of about 30–50 hours. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.

Elderly patients and patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40–60%, and a lower initial dose may be required. A similar increase in AUC was observed in patients with moderate to severe heart failure.

Pediatric Patients: Sixty-two hypertensive patients aged 6 to 17 years received doses of NORVASC between 1.25 mg and 20 mg. Weight-adjusted clearance and volume of distribution were similar to values in adults.

Pharmacodynamics

Hemodynamics Following administration of therapeutic doses to patients with hypertension, NORVASC produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute intravenous administration of amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic oral administration of amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.

With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with NORVASC is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105–114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90–104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressures (+1/-2 mmHg).

In hypertensive patients with normal renal function, therapeutic doses of NORVASC resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with NORVASC have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, NORVASC has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when co-administered with beta-blockers to man. Similar findings, however, have been observed in normals or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

Electrophysiologic Effects: NORVASC does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving NORVASC and concomitant beta blockers. In clinical studies in which NORVASC was

administered in com-bination with beta-blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed. In clinical trials with angina patients alone, NORVASC therapy did not alter electrocardiographic intervals or produce higher degrees of AV blocks.

Clinical Studies

Effects in Hypertension

Adult Patients: The antihypertensive efficacy of NORVASC has been demonstrated in a total of 15 double-blind, placebo-controlled, randomized studies involving 800 patients on NORVASC and 538 on placebo. Once daily administration produced statistically significant placebo-corrected reductions in supine and standing blood pressures at 24 hours postdose, averaging about 12/6 mmHg in the standing position and 13/7 mmHg in the supine position in patients with mild to moderate hypertension. Maintenance of the blood pressure effect over the 24-hour dosing interval was observed, with little difference in peak and trough effect. Tolerance was not demonstrated in patients studied for up to 1 year. The 3 parallel, fixed dose, dose response studies showed that the reduction in supine and standing blood pressures was dose-related within the recommended dosing range. Effects on diastolic pressure were similar in young and older patients. The effect on systolic pressure was greater in older patients, perhaps because of greater baseline systolic pressure. Effects were similar in black patients and in white patients.

Pediatric Patients: Two hundred sixty-eight hypertensive patients aged 6 to 17 years were randomized first to NORVASC 2.5 or 5 mg once daily for 4 weeks and then randomized again to the same dose or to placebo for another 4 weeks. Patients receiving 5 mg at the end of 8 weeks had lower blood pressure than those secondarily randomized to placebo. The magnitude of the treatment effect is difficult to interpret, but it is probably less than 5 mmHg systolic on the 5 mg dose. Adverse events were similar to those seen in adults.

Effects in Chronic Stable Angina:

The effectiveness of 5-10 mg/day of NORVASC in exercise-induced angina has been evaluated in 8 placebo-controlled, double-blind clinical trials of up to 6 weeks duration involving 1038 patients (684 NORVASC, 354 placebo) with chronic stable angina. In 5 of the 8 studies significant increases in exercise time (bicycle or treadmill) were seen with the 10 mg dose. Increases in symptom-limited exercise time averaged 12.8% (63 sec) for NORVASC 10 mg, and averaged 7.9% (38 sec) for NORVASC 5 mg. NORVASC 10 mg also increased time to 1 mm ST segment deviation in several studies and decreased angina attack rate. The sustained efficacy of NORVASC in angina patients has been demonstrated over long-term dosing. In patients with angina there were no clinically significant reductions in blood pressures (4/1 mmHg) or changes in heart rate (+0.3 bpm).

Effects in Vasospastic Angina:

In a double-blind, placebo-controlled clinical trial of 4 weeks duration in 50 patients, NORVASC therapy decreased attacks by approximately 4/week compared with a placebo decrease of approximately 1/week ($p<0.01$). Two of 23 NORVASC and 7 of 27 placebo patients discontinued from the study due to lack of clinical improvement.

Studies in Patients with Congestive Heart Failure:

NORVASC has been compared to placebo in four 8-12 week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or left ventricular ejection fraction. In a long-term (follow-up at least 6 months, mean 13.8 months) placebo-controlled mortality/morbidity study of NORVASC 5-10 mg in 1153 patients with NYHA classes III (n=931) or IV (n=222) heart failure on stable doses of diuretics, digoxin, and ACE inhibitors, NORVASC had no effect on the primary endpoint of the study which was the combined endpoint of all-cause mortality and cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure), or on NYHA classification, or symptoms of heart failure. Total combined all-cause mortality and cardiac morbidity events were 222/571 (39%) for patients on NORVASC and 246/583 (42%) for patients on placebo; the cardiac morbid events represented about 25% of the endpoints in the study.

Another study (PRAISE-2) randomized patients with NYHA class III (80%) or IV (20%) heart failure without clinical symptoms or objective evidence of underlying ischemic disease, on stable doses of ACE inhibitor (99%), digitalis (99%) and diuretics (99%), to placebo (n=827) or NORVASC (n=827) and followed them for a mean of 33 months. There was no statistically significant difference between NORVASC and placebo in the primary endpoint of all cause mortality (95% confidence limits from 8% reduction to 29% increase on NORVASC). With NORVASC there were more reports of pulmonary edema.

INDICATIONS AND USAGE

Hypertension
NORVASC is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.Chronic Stable Angina
NORVASC is indicated for the treatment of chronic stable angina. NORVASC may be used alone or in combination with other antianginal agents.Vasospastic Angina (Prinzmetal's or Variant Angina)
NORVASC is indicated for the treatment of confirmed or suspected vasospastic angina. NORVASC may be used as monotherapy or in combination with other antianginal drugs.

CONTRAINDICATIONS

NORVASC is contraindicated in patients with known sensitivity to amlodipine.

WARNINGS

Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

PRECAUTIONS

General: Since the vasodilation induced by NORVASC is gradual in onset, acute hypotension has rarely been reported after oral administration. Nonetheless, caution, as with any other peripheral vasodilator, should be exercised when administering NORVASC, particularly in patients with severe aortic stenosis.

Use in Patients with Congestive Heart Failure: In general, calcium channel blockers should be used with caution in patients with heart failure. NORVASC (5-10 mg per day) has been studied in a placebo-controlled trial of 1153 patients with NYHA Class III or IV heart failure (see CLINICAL PHARMACOLOGY) on stable doses of ACE inhibitor, digoxin, and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure). NORVASC has been compared to placebo in four 8-12 week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF.

Beta-Blocker Withdrawal: NORVASC is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker.

Patients with Hepatic Failure: Since NORVASC is extensively metabolized by the liver and the plasma elimination half-life (t 1/2) is 56 hours in patients with impaired hepatic function, caution should be exercised when administering NORVASC to patients with severe hepatic impairment.

Drug Interactions: *In vitro* data indicate that NORVASC has no effect on the human plasma protein binding of digoxin, phenytoin, warfarin, and indomethacin.

Effect of other agents on NORVASC.

CIMETIDINE: Co-administration of NORVASC with cimetidine did not alter the pharmacokinetics of NORVASC.

GRAPEFRUIT JUICE: Co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

MAALOX (antacid): Co-administration of the antacid Maalox with a single dose of NORVASC had no significant effect on the pharmacokinetics of NORVASC.

SILDENAFIL: A single 100 mg dose of sildenafil (Viagra[(R)]) in subjects with essential hypertension had no effect on the pharmacokinetic parameters of NORVASC. When NORVASC and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Effect of NORVASC on other agents.

ATORVASTATIN: Co-administration of multiple 10 mg doses of NORVASC with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.

DIGOXIN: Co-administration of NORVASC with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

ETHANOL (alcohol): Single and multiple 10 mg doses of NORVASC had no significant effect on the pharmacokinetics of ethanol.

WARFARIN: Co-administration of NORVASC with warfarin did not change the warfarin prothrombin response time.

In clinical trials, NORVASC has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 amlodipine mg/kg/day showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m[2] basis, similar to the maximum recommended human dose of 10 mg amlodipine/day [*] . For the rat, the highest dose was, on a mg/m[2] basis, about twice the maximum recommended human dose [*] .

Mutagenicity studies conducted with amlodipine maleate revealed no drug related effects at either the gene or chromosome levels.

There was no effect on the fertility of rats treated orally with amlodipine (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg amlodipine/kg/day (8 times [*] the maximum recommended human dose of 10 mg/day on a mg/m[2] basis).

Pregnancy Category C: No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate as doses up to 10 mg amlodipine/kg/day (respectively 8 times [*] and 23 times [*] the maximum recommended human dose of 10 mg on a mg/m[2] basis) during their respective periods of major organogenesis. However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats receiving amlodipine maleate at a dose equivalent to 10 mg amlodipine/kg/day for 14 days before mating and throughout mating and gestation. Amlodipine maleate has been shown to prolong both the gestation period and the duration of labor in rats at this dose. There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential

benefit justifies the potential risk to the fetus. [*] Based on patient weight of 50 kg.

Nursing Mothers: It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while NORVASC is administered.

Pediatric Use: The effect of NORVASC on blood pressure in patients less than 6 years of age is not known.

Geriatric Use: Clinical studies of NORVASC did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40–60%, and a lower initial dose may be required (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

NORVASC has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. In general, treatment with NORVASC was well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with NORVASC were of mild or moderate severity. In controlled clinical trials directly comparing NORVASC (N=1730) in doses up to 10 mg to placebo (N=1250), discontinuation of NORVASC due to adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). The most common side effects are headache and edema. The incidence (%) of side effects which occurred in a dose related manner are as follows:

Adverse Event	2.5 mg N=275	5.0 mg N=296	10.0 mg N=268	Placebo N=520
Edema	1.8	3.0	10.8	0.6
Dizziness	1.1	3.4	3.4	1.5
Flushing	0.7	1.4	2.6	0.0
Palpitation	0.7	1.4	4.5	0.6

Other adverse experiences which were not clearly dose related but which were reported with an incidence greater than 1.0% in placebo-controlled clinical trials include the following:

Placebo-Controlled Studies

	NORVASC (%) (N=1730)	PLACEBO (%) (N=1250)
Headache	7.3	7.8
Fatigue	4.5	2.8
Nausea	2.9	1.9
Abdominal Pain	1.6	0.3
Somnolence	1.4	0.6

For several adverse experiences that appear to be drug and dose related, there was a greater incidence in women than men associated with amlodipine treatment as shown in the following table:

	NORVASC		PLACEBO	
Adverse Event	Male=% (N=1218)	Female=% (N=512)	Male=% (N=914)	Female=% (N=336)
Edema	5.6	14.6	1.4	5.1
Flushing	1.5	4.5	0.3	0.9
Palpitations	1.4	3.3	0.9	0.9
Somnolence	1.3	1.6	0.8	0.3

The following events occurred in <1% but >0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis.

Central and Peripheral Nervous System: hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo.

Gastrointestinal: anorexia, constipation, dyspepsia, ** dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia.

General: allergic reaction, asthenia, ** back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease.

Musculoskeletal System: arthralgia, arthrosis, muscle cramps, ** myalgia.

Psychiatric: sexual dysfunction (male ** and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.

Respiratory System: dyspnea, ** epistaxis.

Skin and Appendages: angioedema, erythema multiforme, pruritus, ** rash, ** rash erythematous, rash maculopapular. **These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

Special Senses: abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.

Urinary System: micturition frequency, micturition disorder, nocturia.

Autonomic Nervous System: dry mouth, sweating increased.

Metabolic and Nutritional: hyperglycemia, thirst.

Hemopoietic: leukopenia, purpura, thrombocytopenia.

The following events occurred in <0.1% of patients: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia.

Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such

as myocardial infarction and angina.

NORVASC therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine.

The following postmarketing event has been reported infrequently where a causal relationship is uncertain: gynecomastia. In postmarketing experience, jaundice and he-patic enzyme elevations (mostly consistent with cholestasis or hepatitis) in some cases severe enough to require hos-pitalization have been reported in association with use of amlodipine.

NORVASC has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles.

OVERDOSAGE

Single oral doses of amlodipine equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg or higher in dogs (11 or more time times the maximum recommended human dose on a mg/m[2] basis) caused a marked peripheral vasodilation and hypotension.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of NORVASC is limited. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) was hospitalized, underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A case of accidental drug overdose has been documented in a 19-month-old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae were noted.

If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As NORVASC is highly protein bound, hemodialysis is not likely to be of benefit.

DOSAGE AND ADMINISTRATION

Adults: The usual initial antihypertensive oral dose of NORVASC is 5 mg once daily with a maximum dose of 10 mg once daily. Small, fragile, or elderly individuals, or patients with hepatic insufficiency may be started on 2.5 mg once daily and this dose may be used when adding NORVASC to other antihypertensive therapy.

Dosage should be adjusted according to each patient's need. In general, titration should proceed over 7 to 14 days so that the physician can fully assess the patient's response to each dose level. Titration may proceed more rapidly, however, if clinically warranted, provided the patient is assessed frequently.

The recommended dose for chronic stable or vasospastic angina is 5-10 mg, with the lower dose suggested in the elderly and in patients with hepatic insufficiency. Most patients will require 10 mg for adequate effect. See ADVERSE REACTIONS section for information related to dosage and side effects.

Children: The effective antihypertensive oral dose in pediatric patients ages 6-17 years is 2.5 mg to 5 mg once daily. Doses in excess of 5 mg daily have not been studied in pediatric patients. See CLINICAL PHARMACOLOGY .

Co-administration with Other Antihypertensive and/or Antianginal Drugs: NORVASC has been safely administered with thiazides, ACE inhibitors, beta-blockers, long-acting nitrates, and/or sublingual nitroglycerin.

HOW SUPPLIED

NORVASC[(R)]-2.5 mg Tablets (amlodipine besylate equivalent to 2.5 mg of amlodipine per tablet) are supplied as white, diamond, flat-faced, beveled edged engraved with "NORVASC" on one side and "2.5" on the other side and supplied as follows:

NDC 0069-1520-68 Bottle of 90

NORVASC[(R)]-5 mg Tablets (amlodipine besylate equivalent to 5 mg of amlodipine per tablet) are white, elongated octagon, flat-faced, beveled edged engraved with both "NORVASC" and "5" on one side and plain on the other side and supplied as follows:

NDC 0069-1530-68 Bottle of 90

NDC 0069-1530-41 Unit Dose package of 100

NDC 0069-1530-72 Bottle of 300

NORVASC[(R)]-10 mg Tablets (amlodipine besylate equivalent to 10 mg of amlodipine per tablet) are white, round, flat-faced, beveled edged engraved with both "NORVASC" and "10" on one side and plain on the other side and supplied as follows:

NDC 0069-1540-68 Bottle of 90

NDC 0069-1540-41 Unit Dose package of 100

Store bottles at controlled room temperature, 59 deg. to 86 deg. F (15 deg. to 30 deg. C) and dispense in tight, light-resistant containers (USP).

Pfizer Labs

Division of Pfizer Inc, NY, NY 10017

LAB-0014-4 Revised January 2005

PRODUCT PHOTO(S): NOTE: These photos can be used only for identification by shape, color, and imprint. They do not depict actual *or relative* size.

The product samples shown here have been supplied by the manufacturer and reproduced in full color by PDR as a quick-reference identification aid. While every effort has been made to assure accurate reproduction, please remember that any visual identification should be considered preliminary. In cases of poisoning or suspected overdosage, the drug's identity should be verified by chemical analysis.
See Image

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Serial Number: 74034510

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Registration Date: 1992-07-21

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LAST APPLICANT(S)/OWNER(S) OF RECORD

1. PFIZER INC.

Address:
PFIZER INC.
235 East 42nd Street
New York, NY 10017
United States
Legal Entity Type: Corporation
State or Country of Incorporation: Delaware

GOODS AND/OR SERVICES

International Class: 005
Class Status: Active

an antibiotic preparation
Basis: 1(a)
First Use Date: 1992-03-16
First Use in Commerce Date: 1992-03-16

ADDITIONAL INFORMATION

(NOT AVAILABLE)

MADRID PROTOCOL INFORMATION

(NOT AVAILABLE)

PROSECUTION HISTORY

2005-06-03 - TEAS Change Of Correspondence Received

2002-07-03 - First renewal 10 year

2002-07-03 - Section 8 (10-year) accepted/ Section 9 granted

2002-04-19 - Combined Section 8 (10-year)/Section 9 filed

2002-04-19 - PAPER RECEIVED

1998-03-20 - Section 8 (6-year) accepted & Section 15 acknowledged

1998-02-11 - Section 8 (6-year) and Section 15 Filed

1992-07-21 - Registered - Principal Register

1992-05-22 - Allowed for Registration - Principal Register (SOU accepted)

1992-05-06 - Assigned To Examiner

1992-04-23 - Statement of use processing complete

1992-04-06 - Amendment to Use filed

1992-02-24 - Extension 2 granted

1991-11-18 - Extension 2 filed

1991-04-04 - Extension 1 granted

1991-03-25 - Extension 1 filed

1990-11-27 - Notice of allowance - mailed

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1990-08-09 - Notice of publication

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Physician's Desk Reference for Prescription Drugs

Zithromax for Oral Suspension, 300 mg, 600 mg, 900 mg, 1200 mg(Pfizer)

BODY:

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZITHROMAX[(R)] (azithromycin) and other bacterial drugs, ZITHROMAX (azithromycin) should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

ZITHROMAX (azithromycin tablets and azithromycin for oral suspension) contain the active ingredient azithromycin, an azalide, a subclass of macrolide antibiotics, for oral administration. Azithromycin has the chemical name (*2R,3S,4R,5R,8R, 10R,11R,12S,13S,14R*)-13-(2,6-dide-oxy-3-*C*-methyl-3-*O*-methyl-(alpha)-*L-ribo*-hexopyranosyl)oxy-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-3,4,6-trideoxy-3-(dimethylamino)-(beta)-*D-xylo*-hexopyranosyl oxy-1-oxa-6-azacyclopentadecan-15-one. Azithromycin is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring. Its molecular formula is C[38] H[72] N[2] O[12] , and its molecular weight is 749.00. Azithromycin has the following structural formula:

See Image

Azithromycin, as the dihydrate, is a white crystalline powder with a molecular formula of C[38] H[72] N[2] O[12] *2H[2] O and a molecular weight of 785.0.

ZITHROMAX is supplied for oral administration as film-coated, modified capsular shaped tablets containing azithromycin dihydrate equivalent to either 250 mg or 500 mg azithromycin and the following inactive ingredients: dibasic calcium phosphate anhydrous, pregelatinized starch, sodium croscarmellose, magnesium stearate, sodium lauryl sulfate, hypromellose, lactose, titanium dioxide, triacetin and D&C Red #30 aluminum lake.

ZITHROMAX for oral suspension is supplied in bottles containing azithromycin dihydrate powder equivalent to 300 mg, 600 mg, 900 mg, or 1200 mg azithromycin per bottle and the following inactive ingredients: sucrose; sodium phosphate, tribasic, anhydrous; hydroxypropyl cellulose; xanthan gum; FD&C Red #40; and spray dried artificial cherry, creme de vanilla and banana flavors. After constitution, each 5 mL of suspension contains 100 mg or 200 mg of azithromycin.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Following oral administration of a single 500 mg dose (two 250 mg tablets) to 36 fasted healthy male volunteers, the mean (SD) pharmacokinetic parameters were AUC[0-72] = 4.3 (1.2) micro g*h/mL; C[max] = 0.5 (0.2) micro g/mL; T[max] = 2.2 (0.9) hours.

With a regimen of 500 mg (two 250 mg capsules *) on day 1, followed by 250 mg daily (one 250 mg capsule) on days 2 through 5, the pharmacokinetic parameters of azithromycin in plasma in healthy young adults (18-40 years of age) are portrayed in the chart below. C[min] and C[max] remained essentially unchanged from day 2 through day 5 of therapy.

Pharmacokinetic Parameters (Mean)	Total n=12 Day 1	Day 5
C[max] (micro g/mL)	0.41	0.24
T[max] (h)	2.5	3.2
AUC[0-24] (micro g*h/mL)	2.6	2.1
C[min] (micro g/mL)	0.05	0.05
Urinary Excret. (% dose)	4.5	6.5

*Azithromycin 250 mg tablets are bioequivalent to 250 mg capsules in the fasted state. Azithromycin 250 mg capsules are no longer commercially available.

In a two-way crossover study, 12 adult healthy volunteers (6 males, 6 females) received 1,500 mg of azithromycin administered in single daily doses over either 5 days (two 250 mg tablets on day 1, followed by one 250 mg tablet on days 2-5) or 3 days (500 mg per day for days 1-3). Due to limited serum samples on day 2 (3-day regimen) and days 2-4 (5-day regimen), the serum concentration-time profile of each subject was fit to a 3-compartment model and the AUC[0-(infinity)] for the fitted concentration profile was comparable between the 5-day and 3-day regimens.

	3-Day Regimen		5-Day Regimen	
Pharmacokinetic Parameter mean (SD)	Day 1	Day 3	Day 1	Day 5
C[max] (serum, micro g/mL)	0.44 (0.22)	0.54 (0.25)	0.43 (0.20)	0.24 (0.06)
Serum AUC[0-(infinity)] (micro g*hr/mL)	17.4 (6.2) *		14.9 (3.1) *	
Serum T[1/2]	71.8 hr		68.9 hr	

*Total AUC for the entire 3-day and 5-day regimens

Median azithromycin exposure (AUC[0-288]) in mononuclear (MN) and polymorphonuclear (PMN) leukocytes following either the 5-day or 3-day regimen was more than a 1000-fold and 800-fold greater than in serum, respectively. Administration of the same total dose with either the 5-day or 3-day regimen may be expected to provide comparable concentrations of azithromycin within MN and PMN leukocytes.

Two azithromycin 250 mg tablets are bioequivalent to a single 500 mg tablet.

Absorption

The absolute bioavailability of azithromycin 250 mg capsules is 38%.

In a two-way crossover study in which 12 healthy subjects received a single 500 mg dose of azithromycin (two 250 mg tablets) with or without a high fat meal, food was shown to increase C[max] by 23% but had no effect on AUC.

When azithromycin suspension was administered with food to 28 adult healthy male subjects, C[max] increased by

56% and AUC was unchanged.

The AUC of azithromycin was unaffected by co-administration of an antacid containing aluminum and magnesium hydroxide with azithromycin capsules; however, the C[max] was reduced by 24%. Administration of cimetidine (800 mg) two hours prior to azithromycin had no effect on azithromycin absorption.

Distribution

The serum protein binding of azithromycin is variable in the concentration range approximating human exposure, decreasing from 51% at 0.02 micro g/mL to 7% at 2 micro g/mL.

Following oral administration, azithromycin is widely distributed throughout the body with an apparent steady-state volume of distribution of 31.1 L/kg. Greater azithromycin concentrations in tissues than in plasma or serum were observed. High tissue concentrations should not be interpreted to be quantitatively related to clinical efficacy. The antimicrobial activity of azithromycin is pH related and appears to be reduced with decreasing pH. However, the extensive distribution of drug to tissues may be relevant to clinical activity.

Selected tissue (or fluid) concentration and tissue (or fluid) to plasma/serum concentration ratios are shown in the following table:

AZITHROMYCIN CONCENTRATIONS FOLLOWING A 500 mg DOSE (TWO 250 mg CAPSULES) IN ADULTS[1]

TISSUE OR FLUID	TIME AFTER DOSE (h)	TISSUE OR FLUID CONCENTRATION (micro g/g or micro g/mL)	CORRESPONSING PLASMA OR SERUM LEVEL (micro g/mL)	TISSUE (FLUID) PLASMA (SERUM) RATIO
SKIN	72-96	0.4	0.012	35
LUNG	72-96	4.0	0.012	>100
SPUTUM *	2-4	1.0	0.64	2
SPUTUM **	10-12	2.9	0.1	30
TONSIL ***	9-18	4.5	0.03	>100
TONSIL ***	180	0.9	0.006	>100
CERVIX #	19	2.8	0.04	70

[1] Azithromycin tissue concentrations were originally determined using 250 mg capsules.
* Sample was obtained 2-4 hours after the first dose.
** Sample was obtained 10-12 hours after the first dose.
*** Dosing regimen of two doses of 250 mg each, separated by 12 hours.
# Sample was obtained 19 hours after a single 500 mg dose.

The extensive tissue distribution was confirmed by examination of additional tissues and fluids (bone, ejaculum, prostate, ovary, uterus, salpinx, stomach, liver, and gallbladder). As there are no data from adequate and well-controlled studies of azithromycin treatment of infections in these additional body sites, the clinical importance of these tissue concentration data is unknown.

Following a regimen of 500 mg on the first day and 250 mg daily for 4 days, only very low concentrations were noted in cerebrospinal fluid (less than 0.01 micro g/mL) in the presence of non-inflamed meninges.

Metabolism

In vitro and *in vivo* studies to assess the metabolism of azithromycin have not been performed.

Elimination

Plasma concentrations of azithromycin following single 500 mg oral and i.v. doses declined in a polyphasic pattern with a mean apparent plasma clearance of 630 mL/min and terminal elimination half-life of 68 hours. The prolonged terminal half-life is thought to be due to extensive uptake and subsequent release of drug from tissues.

Biliary excretion of azithromycin, predominantly as unchanged drug, is a major route of elimination. Over the course of a week, approximately 6% of the administered dose appears as unchanged drug in urine.

Special Populations

Renal Insufficiency

Azithromycin pharmacokinetics were investigated in 42 adults (21 to 85 years of age) with varying degrees of renal impairment. Following the oral administration of a single 1,000 mg dose of azithromycin, mean C[max] and AUC[0-120] increased by 5.1% and 4.2%, respectively in subjects with mild to moderate renal impairment (GFR 10 to 80 mL/min) compared to subjects with normal renal function (GFR >80 mL/min). The mean C[max] and AUC[0-120] increased 61% and 35%, respectively in subjects with severe renal impairment (GFR <10 mL/min) compared to subjects with normal renal function (GFR >80 mL/min). (See DOSAGE AND ADMINISTRATION .)

Hepatic Insufficiency

The pharmacokinetics of azithromycin in subjects with hepatic impairment have not been established.

Gender

There are no significant differences in the disposition of azithromycin between male and female subjects. No dosage adjustment is recommended based on gender.

Geriatric Patients

When studied in healthy elderly subjects aged 65 to 85 years, the pharmacokinetic parameters of azithromycin in elderly men were similar to those in young adults; however, in elderly women, although higher peak concentrations (increased by 30 to 50%) were observed, no significant accumulation occurred.

Pediatric Patients

In two clinical studies, azithromycin for oral suspension was dosed at 10 mg/kg on day 1, followed by 5 mg/kg on days 2 through 5 to two groups of pediatric patients (aged 1-5 years and 5-15 years, respectively). The mean pharmacokinetic parameters on day 5 were C[max] =0.216 micro g/mL, T[max] =1.9 hours, and AUC[0-24] =1.822 micro g*hr/mL for the 1-to 5-year-old group and were C[max] =0.383 micro g/mL, T[max] =2.4 hours, and AUC[0-24] =3.109 micro g*hr/mL for the 5-to 15-year-old group.

Two clinical studies were conducted in 68 pediatric patients aged 3-16 years to determine the pharmacokinetics and safety of azithromycin for oral suspension. Azithromycin was administered following a low-fat breakfast.

The first study consisted of 35 pediatric patients treated with 20 mg/kg/day (maximum daily dose 500 mg) for 3 days of whom 34 patients were evaluated for pharmacokinetics.

In the second study, 33 pediatric patients received doses of 12 mg/kg/day (maximum daily dose 500 mg) for 5 days of

whom 31 patients were evaluated for pharmacokinetics.

In both studies, azithromycin concentrations were determined over a 24 hour period following the last daily dose. Patients weighing above 25.0 kg in the 3-day study or 41.7 kg in the 5-day study received the maximum adult daily dose of 500 mg. Eleven patients (weighing 25.0 kg or less) in the first study and 17 patients (weighing 41.7 kg or less) in the second study received a total dose of 60 mg/kg. The following table shows pharmacokinetic data in the subset of pediatric patients who received a total dose of 60 mg/kg.

Pharmacokinetic Parameter	3-Day Regimen (20 mg/kg x 3 days)	5-Day Regimen (12 mg/kg x 5 days)
mean (SD)		
n	11	17
C[max] (micro g/mL)	1.1 (0.4)	0.5 (0.4)
T[max] (hr)	2.7 (1.9)	2.2 (0.8)
AUC[0-24] (micro g*hr/mL)	7.9 (2.9)	3.9 (1.9)

The similarity of the overall exposure (AUC[0-(infinity)]) between the 3-day and 5-day regimens in pediatric patients is unknown.

Single dose pharmacokinetics in pediatric patients given doses of 30 mg/kg have not been studied. (See DOSAGE AND ADMINISTRATION .)

Drug-Drug Interactions

Drug interaction studies were performed with azithromycin and other drugs likely to be co-administered. The effects of co-administration of azithromycin on the pharmacokinetics of other drugs are shown in Table 1 and the effect of other drugs on the pharmacokinetics of azithromycin are shown in Table 2.

Co-administration of azithromycin at therapeutic doses had a modest effect on the pharmacokinetics of the drugs listed in Table 1. No dosage adjustment of drugs listed in Table 1 is recommended when co-administered with azithromycin.

Co-administration of azithromycin with efavirenz or fluconazole had a modest effect on the pharmacokinetics of azithromycin. Nelfinavir significantly increased the C[max] and AUC of azithromycin. No dosage adjustment of azithromycin is recommended when administered with drugs listed in Table 2. (See PRECAUTIONS - Drug Interactions .)

Table 1. Drug Interactions: Pharmacokinetic Parameters for Co-administered Drugs in the Presence of Azithromycin

Co-administered Drug	Dose of Co-administered Drug	Dose of Azithromycin	n	Ratio (with/without azithromycin) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00	
				Mean C[max]	Mean AUC
Atorvastatin	10 mg/day x 8 days	500 mg/day PO on days 6-8	12	0.83 (0.63 to	1.01 (0.81 to

Table 1. Drug Interactions: Pharmacokinetic Parameters for Co-administered Drugs in the Presence of Azithromycin

				1.08)	1.25)
Carbamazepine	200 mg/day x 2 days, then 200 mg BID x 18 days	500 mg/day PO for days 16-18	7	0.97 (0.88 to 1.06)	0.96 (0.88 to 1.06)
Cetirizine	20 mg/day x 11 days	500 mg PO on day 7, then 250 mg day on days 8-11	14	1.03 (0.93 to 1.14)	1.02 (0.92 to 1.13)
Didanosine	200 mg PO BID x 21 days	1,200 mg/day PO on days 8-21	6	1.44 (0.85 to 2.43)	1.14 (0.83 to 1.57)
Efavirenz	400 mg/day x 7 days	600 mg PO on day 7	14	1.04 *	0.95 *
Fluconazole	200 mg PO single dose	1,200 mg PO single dose	18	1.04 (0.98 to 1.11)	1.01 (0.97 to 1.05)
Indinavir	800 mg TID x 5 days	1,200 mg PO on day 5	18	0.96 (0.86 to 1.08)	0.90 (0.81 to 1.00)
Midazolam	15 mg PO on day 3	500 mg/day PO x 3 days	12	1.27 (0.89 to 1.81)	1.26 (1.01 to 1.56)
Nelfinavir	750 mg TID x 11 days	1,200 mg PO on day 9	14	0.90 (0.81 to 1.01)	0.85 (0.78 to 0.93)
Rifabutin	300 mg/day x 10 days	500 mg PO on day 1, then 250 mg/day on days 2-10	6	See footnote below	NA
Sildenafil	100 mg on days 1 and 4	500 mg/day PO x 3 days	12	1.16 (0.86 to 1.57)	0.92 (0.75 to 1.12)
Theophylline	4 mg/kg IV on days 1, 11, 25	500 mg PO on day 7, 250 mg/ day on days 8-11	10	1.19 (1.02 to 1.40)	1.02 (0.86 to 1.22)
Theophylline	300 mg PO BID x 15 days	500 mg PO on day 6, then 250 mg/day on days 7-10	8	1.09 (0.92 to 1.29)	1.08 (0.89 to 1.31)
Triazolam	0.125 mg on day 2	500 mg PO on day 1, then 250 mg/day on day 2	12	1.06 *	1.02 *
Trimethoprim/ Sulfamethoxazole	160 mg/800 mg/day PO x 7 days	1,200 mg PO on day 7	12	0.85 (0.75 to 0.97)/ 0.90 (0.78 to 1.03)	0.87 (0.80 to 0.95)/ 0.96 (0.88 to 1.03)

Table 1. Drug Interactions: Pharmacokinetic Parameters for Co-administered Drugs in the Presence of Azithromycin

Zidovudine	500 mg/day PO x 21 days	600 mg/day PO x 14 days	5	1.12 (0.42 to 3.02)	0.94 (0.52 to 1.70)
Zidovudine	500 mg/day PO x 21 days	1,200 mg/day PO x 14 days	4	1.31 (0.43 to 3.97)	1.30 (0.69 to 2.43)

NA - Not Available
* - 90% Confidence interval not reported

Mean rifabutin concentrations one-half day after the last dose of rifabutin were 60 ng/mL when co-administered with azithromycin and 71 ng/mL when co-administered with placebo.

Table 2. Drug Interactions: Pharmacokinetic Parameters for Azithromycin in the Presence of Co-administered Drugs (See PRECAUTIONS - Drug Interactions .)

Co-administered Drug	Dose of Co-administered Drug	Dose of Azithromycin	n	Ratio (with/without co-administered drug) of Azithromycin Pharmacokinetic Parameters (90% CI); No Effect = 1.00	
				Mean C[max]	Mean AUC
Efavirenz	400 mg/day x 7 days	600 mg PO on day 7	14	1.22 (1.04 to 1.42)	0.92 *
Fluconazole	200 mg PO single dose	1,200 mg PO single dose	18	0.82 (0.66 to 1.02)	1.07 (0.94 to 1.22)
Nelfinavir	750 mg TID x 11 days	1,200 mg PO on day 9	14	2.36 (1.77 to 3.15)	2.12 (1.80 to 2.50)
Rifabutin	300 mg/day x 10 days	500 mg PO on day 1, then 250 mg/day on days 2-10	6	See footnote below	NA

NA - Not available
* - 90% Confidence interval not reported
Mean azithromycin concentrations one day after the last dose were 53 ng/mL when coadministered with 300 mg daily rifabutin and 49 ng/mL when coadministered with placebo.

Microbiology: Azithromycin acts by binding to the 50S ribosomal subunit of susceptible microorganisms and, thus, interfering with microbial protein synthesis. Nucleic acid synthesis is not affected.

Azithromycin concentrates in phagocytes and fibroblasts as demonstrated by *in vitro* incubation techniques. Using such methodology, the ratio of intracellular to extracellular concentration was >30 after one hour incubation. *In vivo* studies suggest that concentration in phagocytes may contribute to drug distribution to inflamed tissues.

Azithromycin has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section.

Aerobic and facultative gram-positive microorganisms

Staphylococcus aureus

Streptococcus agalactiae

Streptococcus pneumoniae

Streptococcus pyogenes

NOTE: Azithromycin demonstrates cross-resistance with erythromycin-resistant gram-positive strains. Most strains of *Enterococcus faecalis* and methicillin-resistant staphylococci are resistant to azithromycin.

Aerobic and facultative gram-negative microorganisms

Haemophilus ducreyi

Haemophilus influenzae

Moraxella catarrhalis

Neisseria gonorrhoeae

"Other" microorganisms

Chlamydia pneumoniae

Chlamydia trachomatis

Mycoplasma pneumoniae

Beta-lactamase production should have no effect on azithromycin activity.

The following *in vitro* data are available, but their clinical significance is unknown .

At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoints for azithromycin. However, the safety and effectiveness of azithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic and facultative gram-positive microorganisms

Streptococci (Groups C, F, G)

Viridans group streptococci

Aerobic and facultative gram-negative microorganisms

Bordetella pertussis

Legionella pneumophila

Anaerobic microorganisms

Peptostreptococcus species

Prevotella bivia

"Other" microorganisms

Ureaplasma urealyticum

Susceptibility Testing Methods:

When available, the results of *in vitro* susceptibility test results for antimicrobial drugs used in resident hospitals should be provided to the physician as periodic reports which describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports may differ from susceptibility data obtained from outpatient use, but could aid the physician in selecting the most effective antimicrobial.

Dilution techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1,3] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of azithromycin powder. The MIC values should be interpreted according to criteria provided in Table 1.

Diffusion techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2,3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15-micro g azithromycin to test the susceptibility of microorganisms to azithromycin. The disk diffusion interpretive criteria are provided in Table 1.

Table 1. Susceptibility Interpretive Criteria for Azithromycin
Susceptibility Test Result Interpretive Criteria

	Minimum Inhibitory Concentrations (micro g/mL)			Disk Diffusion (zone diameters in mm)		
Pathogen	S	I	R[a]	S	I	R[a]
Haemophilus spp.	</= 4	--	--	>/= 12	--	--
Staphylococcus aureus	</= 2	4	>/= 8	>/= 18	14-17	</= 13
Streptococci including S. pneumoniae[b]	</= 0.5	1	>/= 2	>/= 18	14-17	</= 13

[a] The current absence of data on resistant strains precludes defining any category other than "susceptible. " If strains yield MIC results other than susceptible, they should

Table 1. Susceptibility Interpretive Criteria for Azithromycin
Susceptibility Test Result Interpretive Criteria
be submitted to a reference laboratory for further testing.
[b] Susceptibility of streptococci including S. pneumoniae to azithromycin and other macrolides can be predicted by testing erythromycin.

No interpretive criteria have been established for testing *Neisseria gonorrhoeae* . This species is not usually tested.

A report of "susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound reaches the concentrations usually achievable. A report of "intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound reaches the concentrations usually achievable; other therapy should be selected.

QUALITY CONTROL:

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures. Standard azithromycin powder should provide the following range of values noted in Table 2. Quality control microorganisms are specific strains of organisms with intrinsic biological properties. QC strains are very stable strains which will give a standard and repeatable susceptibility pattern. The specific strains used for microbiological quality control are not clinically significant.

Table 2. Acceptable Quality Control Ranges for Azithromycin

QC Strain	Minimum Inhibitory Concentrations (micro g/mL)	Disk Diffusion (zone diameters in mm)
Haemophilus influenzae ATCC 49247	1.0–4.0	13–21
Staphylococcus aureus ATCC 29213	0.5–2.0	
Staphylococcus aureus ATCC 25923		21–26
Streptococcus pneumoniae ATCC 49619	0.06–0.25	19–25

INDICATIONS AND USAGE

ZITHROMAX (azithromycin) is indicated for the treatment of patients with mild to moderate infections (pneumonia: see WARNINGS) caused by susceptible strains of the designated microorganisms in the specific conditions listed below. As recommended dosages, durations of therapy and applicable patient populations vary among these infections, please see DOSAGE AND ADMINISTRATION for specific dosing recommendations .

Adults:

Acute bacterial exacerbations of chronic obstructive pulmonary disease due to *Haemophilus influenzae, Moraxella*

catarrhalis or *Streptococcus pneumoniae* .

Acute bacterial sinusitis due to *Haemophilus influenzae, Moraxella catarrhalis* or *Streptococcus pneumoniae.*

Community-acquired pneumonia due to *Chlamydia pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae* or *Streptococcus pneumoniae* in patients appropriate for oral therapy.

NOTE: Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following:

patients with cystic fibrosis,

patients with nosocomially acquired infections,

patients with known or suspected bacteremia,

patients requiring hospitalization,

elderly or debilitated patients, or

patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

Pharyngitis/tonsillitis caused by *Streptococcus pyogenes* as an alternative to first-line therapy in individuals who cannot use first-line therapy.

NOTE: Penicillin by the intramuscular route is the usual drug of choice in the treatment of *Streptococcus pyogenes* infection and the prophylaxis of rheumatic fever. ZITHROMAX is often effective in the eradication of susceptible strains of *Streptococcus pyogenes* from the nasopharynx. Because some strains are resistant to ZITHROMAX, susceptibility tests should be performed when patients are treated with ZITHROMAX. Data establishing efficacy of azithromycin in subsequent prevention of rheumatic fever are not available.

Uncomplicated skin and skin structure infections due to *Staphylococcus aureus, Streptococcus pyogenes* , or *Streptococcus agalactiae* . Abscesses usually require surgical drainage.

Urethritis and cervicitis due to *Chlamydia trachomatis* or *Neisseria gonorrhoeae* .

Genital ulcer disease in men due to *Haemophilus ducreyi* (chancroid). Due to the small number of women included in clinical trials, the efficacy of azithromycin in the treatment of chancroid in women has not been established.

ZITHROMAX, at the recommended dose, should not be relied upon to treat syphilis. Antimicrobial agents used in high doses for short periods of time to treat non-gonococcal urethritis may mask or delay the symptoms of incubating syphilis. All patients with sexually-transmitted urethritis or cervicitis should have a serologic test for syphilis and appropriate cultures for gonorrhea performed at the time of diagnosis. Appropriate antimicrobial therapy and follow-up tests for these diseases should be initiated if infection is confirmed.

Appropriate culture and susceptibility tests should be performed before treatment to determine the causative organism and its susceptibility to azithromycin. Therapy with ZITHROMAX may be initiated before results of these tests are known; once the results become available, antimicrobial therapy should be adjusted accordingly.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZITHROMAX (azithromycin) and other antibacterial drugs, ZITHROMAX (azithromycin) should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local

epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Pediatric Patients: (See PRECAUTIONS — Pediatric Use and CLINICAL STUDIES IN PEDIATRIC PATIENTS .)

Acute otitis media caused by *Haemophilus influenzae, Moraxella catarrhalis* or *Streptococcus pneumoniae* . (For specific dosage recommendation, see DOSAGE AND ADMINISTRATION .)

Community-acquired pneumonia due to *Chlamydia pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae* or *Streptococcus pneumoniae* in patients appropriate for oral therapy. (For specific dosage recommendation, see DOSAGE AND ADMINISTRATION .)

NOTE: Azithromycin should not be used in pediatric patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following:

patients with cystic fibrosis,

patients with nosocomially acquired infections,

patients with known or suspected bacteremia,

patients requiring hospitalization, or

patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

Pharyngitis/tonsillitis caused by *Streptococcus pyogenes* as an alternative to first-line therapy in individuals who cannot use first-line therapy. (For specific dosage recommendation, see DOSAGE AND ADMINISTRATION .)

NOTE: Penicillin by the intramuscular route is the usual drug of choice in the treatment of *Streptococcus pyogenes* infection and the prophylaxis of rheumatic fever. ZITHROMAX is often effective in the eradication of susceptible strains of *Streptococcus pyogenes* from the nasopharynx. Because some strains are resistant to ZITHROMAX, susceptibility tests should be performed when patients are treated with ZITHROMAX. Data establishing efficacy of azithromycin in subsequent prevention of rheumatic fever are not available.

Appropriate culture and susceptibility tests should be performed before treatment to determine the causative organism and its susceptibility to azithromycin. Therapy with ZITHROMAX may be initiated before results of these tests are known; once the results become available, antimicrobial therapy should be adjusted accordingly.

CONTRAINDICATIONS

ZITHROMAX is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin or any macrolide antibiotic.

WARNINGS

Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Stevens Johnson Syndrome and toxic epidermal necrolysis have been reported rarely in patients on azithromycin therapy. Although rare, fatalities have been reported. (See CONTRAINDICATIONS .) Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms recurred soon thereafter in some patients without further azithromycin exposure. These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long tissue half-life of azithromycin and subsequent prolonged exposure to antigen is unknown at present.

If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians

should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

In the treatment of pneumonia, azithromycin has only been shown to be safe and effective in the treatment of community-acquired pneumonia due to *Chlamydia pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae* or *Streptococcus pneumoniae* in patients appropriate for oral therapy. Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following: patients with cystic fibrosis, patients with nosocomially acquired infections, patients with known or suspected bacteremia, patients requiring hospitalization, elderly or debilitated patients, or patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

General: Because azithromycin is principally eliminated via the liver, caution should be exercised when azithromycin is administered to patients with impaired hepatic function. Due to the limited data in subjects with GFR <10 mL/min, caution should be exercised when prescribing azithromycin in these patients. (See CLINICAL PHARMACOLOGY - Special Populations - Renal Insufficiency .)

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and *torsades de pointes* , have been seen in treatment with other macrolides. A similar effect with azithromycin cannot be completely ruled out in patients at increased risk for prolonged cardiac repolarization.

Prescribing ZITHROMAX (azithromycin) in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Information for Patients:

ZITHROMAX tablets and oral suspension can be taken with or without food.

Patients should also be cautioned not to take aluminum-and magnesium-containing antacids and azithromycin simultaneously.

The patient should be directed to discontinue azithromycin immediately and contact a physician if any signs of an allergic reaction occur.

Patients should be counseled that antibacterial drugs including ZITHROMAX (azithromycin) should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When ZITHROMAX (azithromycin) is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of the therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by ZITHROMAX (azithromycin) or other

antibacterial drugs in the future.

Drug Interactions:

Co-administration of nelfinavir at steady-state with a single oral dose of azithromycin resulted in increased azithromycin serum concentrations. Although a dose adjustment of azithromycin is not recommended when administered in combination with nelfinavir, close monitoring for known side effects of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted. (See ADVERSE REACTIONS .)

Azithromycin did not affect the prothrombin time response to a single dose of warfarin. However, prudent medical practice dictates careful monitoring of prothrombin time in all patients treated with azithromycin and warfarin concomitantly. Concurrent use of macrolides and warfarin in clinical practice has been associated with increased anticoagulant effects.

Drug interaction studies were performed with azithromycin and other drugs likely to be co-administered. (See CLINICAL PHARMACOLOGY - Drug-Drug Interactions .) When used in therapeutic doses, azithromycin had a modest effect on the pharmacokinetics of atorvastatin, carbamazepine, cetirizine, didanosine, efavirenz, fluconazole, indinavir, midazolam, rifabutin, sildenafil, theophylline (intravenous and oral), triazolam, trimethoprim/sulfamethoxazole or zidovudine. Co-administration with efavirenz, or fluconazole had a modest effect on the pharmacokinetics of azithromycin. No dosage adjustment of either drug is recommended when azithromycin is coadministered with any of the above agents.

Interactions with the drugs listed below have not been reported in clinical trials with azithromycin; however, no specific drug interaction studies have been performed to evaluate potential drug-drug interaction. Nonetheless, they have been observed with macrolide products. Until further data are developed regarding drug interactions when azithromycin and these drugs are used concomitantly, careful monitoring of patients is advised:

Digoxin-elevated digoxin concentrations.

Ergotamine or dihydroergotamine-acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.

Terfenadine, cyclosporine, hexobarbital and phenytoin concentrations.

Laboratory Test Interactions: There are no reported laboratory test interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic potential. Azithromycin has shown no mutagenic potential in standard laboratory tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay. No evidence of impaired fertility due to azithromycin was found.

Pregnancy: Teratogenic Effects. Pregnancy Category B: Reproduction studies have been performed in rats and mice at doses up to moderately maternally toxic dose concentrations (i.e., 200 mg/kg/day). These doses, based on a mg/m[2] basis, are estimated to be 4 and 2 times, respectively, the human daily dose of 500 mg. In the animal studies, no evidence of harm to the fetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed.

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

Pediatric Use: (See CLINICAL PHARMACOLOGY , INDICATIONS AND USAGE , and DOSAGE AND ADMINISTRATION .)

Acute Otitis Media (total dosage regimen: 30 mg/kg, see DOSAGE AND ADMINISTRATION): Safety and

effectiveness in the treatment of pediatric patients with otitis media under 6 months of age have not been established.

Acute Bacterial Sinusitis (dosage regimen: 10 mg/kg on Days 1-3): Safety and effectiveness in the treatment of pediatric patients with acute bacterial sinusitis under 6 months of age have not been established. Use of Zithromax[(R)] for the treatment of acute bacterial sinusitis pediatric patients (6 months of age or greater) is supported by adequate and well-controlled studies in adults, similar pathophysiology of acute sinusitis in adults and pediatric patients, and studies of acute otitis media in pediatric patients.

Community-Acquired Pneumonia (dosage regimen: 10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5): Safety and effectiveness in the treatment of pediatric patients with community-acquired pneumonia under 6 months of age have not been established. Safety and effectiveness for pneumonia due to *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* were documented in pediatric clinical trials. Safety and effectiveness for pneumonia due to *Haemophilus influenzae* and *Streptococcus pneumoniae* were not documented bacteriologically in the pediatric clinical trial due to difficulty in obtaining specimens. Use of azithromycin for these two microorganisms is supported, however, by evidence from adequate and well-controlled studies in adults.

Pharyngitis/Tonsillitis (dosage regimen: 12 mg/kg on Days 1-5): Safety and effectiveness in the treatment of pediatric patients with pharyngitis/tonsillitis under 2 years of age have not been established.

Studies evaluating the use of repeated courses of therapy have not been conducted. (See CLINICAL PHARMACOLOGY and ANIMAL TOXICOLOGY .)

Geriatric Use: Pharmacokinetic parameters in older volunteers (65-85 years old) were similar to those in younger volunteers (18-40 years old) for the 5-day therapeutic regimen. Dosage adjustment does not appear to be necessary for older patients with normal renal and hepatic function receiving treatment with this dosage regimen. (See CLINICAL PHARMACOLOGY .)

In multiple-dose clinical trials of oral azithromycin, 9% of patients were at least 65 years of age (458/4949) and 3% of patients (144/4949) were at least 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ZITHROMAX 250 mg tablets contain 0.9 mg of sodium per tablet.

ZITHROMAX 500 mg tablets contain 1.8 mg of sodium per tablet.

ZITHROMAX for oral suspension 100 mg/5 mL contains 3.7 mg of sodium per 5 mL of constituted solution.

ZITHROMAX for oral suspension 200 mg/5 mL contains 7.4 mg of sodium per 5 mL of constituted solution.

ADVERSE REACTIONS

In clinical trials, most of the reported side effects were mild to moderate in severity and were reversible upon discontinuation of the drug. Potentially serious side effects of angioedema and cholestatic jaundice were reported rarely. Approximately 0.7% of the patients (adults and pediatric patients) from the 5-day multiple-dose clinical trials discontinued ZITHROMAX (azithromycin) therapy because of treatment-related side effects. In adults given 500 mg/day for 3 days, the discontinuation rate due to treatment-related side effects was 0.6%. In clinical trials in pediatric patients given 30 mg/kg, either as a single dose or over 3 days, discontinuation from the trials due to treatment-related side effects was approximately 1%. (See DOSAGE AND ADMINISTRATION .) Most of the side effects leading to discontinuation were related to the gastrointestinal tract, e.g., nausea, vomiting, diarrhea, or abdominal pain. (See CLINICAL STUDIES IN PEDIATRIC PATIENTS .)

Clinical:

Adults:

Multiple-dose regimens: Overall, the most common treatment-related side effects in adult patients receiving multiple-dose regimens of ZITHROMAX were related to the gastrointestinal system with diarrhea/loose stools (4-5%), nausea (3%) and abdominal pain (2-3%) being the most frequently reported.

No other treatment-related side effects occurred in patients on the multiple-dose regimens of ZITHROMAX with a frequency greater than 1%. Side effects that occurred with a frequency of 1% or less included the following:

Cardiovascular: Palpitations, chest pain.

Gastrointestinal: Dyspepsia, flatulence, vomiting, melena and cholestatic jaundice.

Genitourinary: Monilia, vaginitis and nephritis.

Nervous System: Dizziness, headache, vertigo and somnolence.

General: Fatigue.

Allergic: Rash, pruritus, photosensitivity and angioedema.

Single 1-gram dose regimen: Overall, the most common side effects in patients receiving a single-dose regimen of 1 gram of ZITHROMAX were related to the gastrointestinal system and were more frequently reported than in patients receiving the multiple-dose regimen.

Side effects that occurred in patients on the single one-gram dosing regimen of ZITHROMAX with a frequency of 1% or greater included diarrhea/loose stools (7%), nausea (5%), abdominal pain (5%), vomiting (2%), dyspepsia (1%) and vaginitis (1%).

Single 2-gram dose regimen: Overall, the most common side effects in patients receiving a single 2-gram dose of ZITHROMAX were related to the gastrointestinal system. Side effects that occurred in patients in this study with a frequency of 1% or greater included nausea (18%), diarrhea/loose stools (14%), vomiting (7%), abdominal pain (7%), vaginitis (2%), dyspepsia (1%) and dizziness (1%). The majority of these complaints were mild in nature.

Pediatric Patients:

Single and Multiple-dose regimens: The types of side effects in pediatric patients were comparable to those seen in adults, with different incidence rates for the dosage regimens recommended in pediatric patients.

Acute Otitis Media: For the recommended total dosage regimen of 30 mg/kg, the most frequent side effects (>/=1%) attributed to treatment were diarrhea, abdominal pain, vomiting, nausea and rash. (See DOSAGE AND ADMINISTRATION and CLINICAL STUDIES IN PEDIATRIC PATIENTS .)

The incidence, based on dosing regimen, is described in the table below:

Dosage Regimen	Diarrhea, %	Abdominal Pain, %	Vomiting, %	Nausea, %	Rash, %
1-day	4.3%	1.4%	4.9%	1.0%	1.0%
3-day	2.6%	1.7%	2.3%	0.4%	0.6%
5-day	1.8%	1.2%	1.1%	0.5%	0.4%

Community-Acquired Pneumonia: For the recommended dosage regimen of 10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5, the most frequent side effects attributed to treatment were diarrhea/loose stools, abdominal pain, vomiting, nausea and rash.

The incidence is described in the table below:

Dosage Regimen	Diarrhea/Loose stools, %	Abdominal Pain, %	Vomiting, %	Nausea, %	Rash, %
5-day	5.8%	1.9%	1.9%	1.9%	1.6%

Pharyngitis/tonsillitis: For the recommended dosage regimen of 12 mg/kg on Days 1-5, the most frequent side effects attributed to treatment were diarrhea, vomiting, abdominal pain, nausea and headache.

The incidence is described in the table below:

Dosage Regimen	Diarrhea, %	Abdominal Pain, %	Vomiting, %	Nausea, %	Rash, %	Headache, %
5-day	5.4%	3.4%	5.6%	1.8%	0.7%	1.1%

With any of the treatment regimens, no other treatment-related side effects occurred in pediatric patients treated with ZITHROMAX with a frequency greater than 1%. Side effects that occurred with a frequency of 1% or less included the following:

Cardiovascular: Chest pain.

Gastrointestinal: Dyspepsia, constipation, anorexia, enteritis, flatulence, gastritis, jaundice, loose stools and oral moniliasis.

Hematologic and Lymphatic: Anemia and leukopenia.

Nervous System: Headache (otitis media dosage), hyperkinesia, dizziness, agitation, nervousness and insomnia.

General: Fever, face edema, fatigue, fungal infection, malaise and pain.

Allergic: Rash and allergic reaction.

Respiratory: Cough increased, pharyngitis, pleural effusion and rhinitis.

Skin and Appendages: Eczema, fungal dermatitis, pruritus, sweating, urticaria and vesiculobullous rash.

Special Senses: Conjunctivitis.

Post-Marketing Experience:

Adverse events reported with azithromycin during the post-marketing period in adult and/or pediatric patients for which a causal relationship may not be established include:

Allergic: Arthralgia, edema, urticaria and angioedema.

Cardiovascular: Arrhythmias including ventricular tachycardia and hypotension. There have been rare reports of QT prolongation and *torsades de pointes* .

Gastrointestinal: Anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea rarely resulting in dehydration, pseudomembranous colitis, pancreatitis, oral candidiasis and rare reports of tongue discoloration.

General: Asthenia, paresthesia, fatigue, malaise and anaphylaxis (rarely fatal).

Genitourinary: Interstitial nephritis and acute renal failure and vaginitis.

Hematopoietic: Thrombocytopenia.

Liver/Biliary: Abnormal liver function including hepatitis and cholestatic jaundice, as well as rare cases of hepatic necrosis and hepatic failure, some of which have resulted in death.

Nervous System: Convulsions, dizziness/vertigo, headache, somnolence, hyperactivity, nervousness, agitation and syncope.

Psychiatric: Aggressive reaction and anxiety.

Skin/Appendages: Pruritus, rarely serious skin reactions including erythema multiforme, Stevens Johnson Syndrome and toxic epidermal necrolysis.

Special Senses: Hearing disturbances including hearing loss, deafness and/or tinnitus and rare reports of taste perversion.

Laboratory Abnormalities:

Adults:

Clinically significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows: with an incidence of greater than 1%: decreased hemoglobin, hematocrit, lymphocytes, neutrophils and blood glucose; elevated serum creatine phosphokinase, potassium, ALT, GGT, AST, BUN, creatinine, blood glucose, platelet count, lymphocytes, neutrophils and eosinophils; with an incidence of less than 1%: leukopenia, neutropenia, decreased sodium, potassium, platelet count, elevated monocytes, basophils, bicarbonate, serum alkaline phosphatase, bilirubin, LDH and phosphate. The majority of subjects with elevated serum creatinine also had abnormal values at baseline.

When follow-up was provided, changes in laboratory tests appeared to be reversible.

In multiple-dose clinical trials involving more than 5000 patients, four patients discontinued therapy because of treatment-related liver enzyme abnormalities and one because of a renal function abnormality.

Pediatric Patients:

One, Three and Five Day Regimens

Laboratory data collected from comparative clinical trials employing two 3-day regimens (30 mg/kg or 60 mg/kg in divided doses over 3 days), or two 5-day regimens (30 mg/kg or 60 mg/kg in divided doses over 5 days) were similar

for regimens of azithromycin and all comparators combined, with most clinically significant laboratory abnormalities occurring at incidences of 1-5%. Laboratory data for patients receiving 30 mg/kg as a single dose were collected in one single center trial. In that trial, an absolute neutrophil count between 500-1500 cells/mm[3] was observed in 10/64 patients receiving 30 mg/kg as a single dose, 9/62 patients receiving 30 mg/kg given over 3 days, and 8/63 comparator patients. No patient had an absolute neutrophil count <500 cells/mm[3] . (See DOSAGE AND ADMINISTRATION .)

In multiple-dose clinical trials involving approximately 4700 pediatric patients, no patients discontinued therapy because of treatment-related laboratory abnormalities.

DOSAGE AND ADMINISTRATION

(See INDICATIONS AND USAGE and CLINICAL PHARMACOLOGY .)

Adults:

Infection *	Recommended Dose/Duration of Therapy
Community-acquired pneumonia (mild severity) Pharyngitis/tonsillitis (second line therapy) Skin/skin structure (uncomplicated)	500 mg as a single dose on Day 1, followed by 250 mg once daily on Days 2 through 5.
Acute bacterial exacerbations of chronic obstructive pulmonary disease (mild to moderate)	500 mg QD x 3 days OR 500 mg as a single dose on Day 1, followed by 250 mg once daily on Days 2 through 5.
Acute bacterial sinusitis	500 mg QD x 3 days
Genital ulcer disease (chancroid)	One single 1 gram dose
Non-gonococcal urethritis and cervicitis	One single 1 gram dose
Gonococcal urethritis and cervicitis	One single 2 gram dose

* DUE TO THE INDICATED ORGANISMS (See INDICATIONS AND USAGE .)

ZITHROMAX[(R)] tablets can be taken with or without food.

Renal Insufficiency:

No dosage adjustment is recommended for subjects with renal impairment (GFR </=80 mL/min). The mean AUC[0-120] was similar in subjects with GFR 10-80 mL/min compared to subjects with normal renal function, whereas it increased 35% in subjects with GFR <10 mL/min compared to subjects with normal renal function. Caution should be exercised when azithromycin is administered to subjects with severe renal impairment. (See CLINICAL PHARMACOLOGY , Special Populations , Renal Insufficiency .)

Hepatic Insufficiency:

The pharmacokinetics of azithromycin in subjects with hepatic impairment have not been established. No dose adjustment recommendations can be made in patients with impaired hepatic function (See CLINICAL PHARMACOLOGY , Special Populations , Hepatic Insufficiency .)

No dosage adjustment is recommended based on age or gender. (See CLINICAL PHARMACOLOGY , Special

Populations .)

Pediatric Patients:

ZITHROMAX for oral suspension can be taken with or without food.

Acute Otitis Media: The recommended dose of ZITHROMAX for oral suspension for the treatment of pediatric patients with acute otitis media is 30 mg/kg given as a single dose or 10 mg/kg once daily for 3 days or 10 mg/kg as a single dose on the first day followed by 5 mg/kg/day on Days 2 through 5. (See chart below.)

Acute Bacterial Sinusitis: The recommended dose of ZITHROMAX[(R)] for oral suspension for the treatment of pediatric patients with acute bacterial sinusitis is 10 mg/kg once daily for 3 days. (See chart below.)

Community-Acquired Pneumonia: The recommended dose of ZITHROMAX for oral suspension for the treatment of pediatric patients with community-acquired pneumonia is 10 mg/kg as a single dose on the first day followed by 5 mg/kg on Days 2 through 5. (See chart below.)

PEDIATRIC DOSAGE GUIDELINES FOR OTITIS MEDIA, ACUTE BACTERIAL SINUSITIS AND COMMUNITY-ACQUIRED PNEUMONIA (Age 6 months and above, see PRECAUTIONS —Pediatric Use.) Based on Body Weight

OTITIS MEDIA AND COMMUNITY-ACQUIRED PNEUMONIA: (5-Day Regimen) *
Dosing Calculated on 10 mg/kg/day Day 1 and 5 mg/kg/day Days 2 to 5.

Weight		100 mg/5 mL		200 mg/5 mL		Total mL per Treatment Course	Total mg per Treatment Course
Kg	Lbs.	Day 1	Days 2–5	Day 1	Days 2–5		
5	11	2.5 mL (1/2 tsp)	1.25 mL (1/4 tsp)			7.5 mL	150 mg
10	22	5 mL (1 tsp)	2.5 mL (1/2 tsp)			15 mL	300 mg
20	44			5 mL (1 tsp)	2.5 mL (1/2 tsp)	15 mL	600 mg
30	66			7.5 mL (1 1/2 tsp)	3.75 mL (3/4 tsp)	22.5 mL	900 mg
40	88			10 mL (2 tsp)	5 mL (1 tsp)	30 mL	1200 mg
50 and above	110 and above			12.5 mL (2 1/2 tsp)	6.25 mL (1 1/4 tsp)	37.5 mL	1500 mg

*Effectiveness of the 3-day or 1-day regimen in pediatric patients with

PEDIATRIC DOSAGE GUIDELINES FOR OTITIS MEDIA, ACUTE BACTERIAL SINUSITIS AND COMMUNITY-ACQUIRED PNEUMONIA (Age 6 months and above, see PRECAUTIONS —Pediatric Use.) Based on Body Weight

community-acquired pneumonia has not been established.

OTITIS MEDIA AND ACUTE BACTERIAL SINUSITIS: (3-Day Regimen) *

Weight		Dosing Calculated on 10 mg/kg/day 100 mg/5 mL	200 mg/5 mL	Total mL per Treatment Course	Total mg per Treatment Course
Kg	Lbs.	Day 1-3	Day 1-3		
5	11	2.5 mL (1/2 tsp)		7.5 mL	150 mg
10	22	5 mL (1 tsp)		15 mL	300 mg
20	44		5 mL (1 tsp)	15 mL	600 mg
30	66		7.5 mL (1 1/2 tsp)	22.5 mL	900 mg
40	88		10 mL (2 tsp)	30 mL	1200 mg
50 and above	110 and above		12.5 mL (2 1/2 tsp)	37.5 mL	1500 mg

*Effectiveness of the 5-day or 1-day regimen in pediatric patients with acute bacterial sinusitis has not been established.

OTITIS MEDIA: (1-Day Regimen)

Weight		Dosing Calculated on 30 mg/kg as a single dose 200 mg/5 mL	Total mL per Treatment Course	Total mg per Treatment Course
Kg	Lbs.	Day 1		
5	11	3.75 mL (3/4 tsp)	3.75 mL	150 mg
10	22	7.5 mL (1 1/2 tsp)	7.5 mL	300 mg
20	44	15 mL (3 tsp)	15 mL	600 mg
30	66	22.5 mL (4 1/2 tsp)	22.5 mL	900 mg
40	88	30 mL (6 tsp)	30 mL	1200 mg
50 and above	110 and above	37.5 mL (7 1/2 tsp)	37.5 mL	1500 mg

The safety of re-dosing azithromycin in pediatric patients who vomit after receiving 30 mg/kg as a single dose has not been established. In clinical studies involving 487 patients with acute otitis media given a single 30 mg/kg dose of azithromycin, eight patients who vomited within 30 minutes of dosing were re-dosed at the same total dose.

Pharyngitis/Tonsillitis: The recommended dose of ZITHROMAX for children with pharyngitis/tonsillitis is 12 mg/kg once daily for 5 days. (See chart below.)

PEDIATRIC DOSAGE GUIDELINES FOR PHARYNGITIS/TONSILLITIS (Age 2 years and above, see PRECAUTIONS—Pediatric Use.) Based on Body Weight

PHARYNGITIS/TONSILLITIS: (5-Day Regimen)
Dosing Calculated on 12 mg/kg/day for 5 days.

Weight		200 mg/5 mL	Total mL per Treatment Course	Total mg per Treatment Course
Kg	Lbs.	Day 1-5		
8	18	2.5 mL (1/2 tsp)	12.5 mL	500 mg
17	37	5 mL (1 tsp)	25 mL	1000 mg
25	55	7.5 mL (1 1/2 tsp)	37.5 mL	1500 mg
33	73	10 mL (2 tsp)	50 mL	2000 mg
40	88	12.5 mL (2 1/2 tsp)	62.5 mL	2500 mg

Constituting instructions for ZITHROMAX Oral Suspension, 300, 600, 900, 1200 mg bottles. The table below indicates the volume of water to be used for constitution:

Amount of water to be added	Total volume after constitution (azithromycin content)	Azithromycin concentration after constitution
9 mL (300 mg)	15 mL (300 mg)	100 mg/5 mL
9 mL (600 mg)	15 mL (600 mg)	200 mg/5 mL
12 mL (900 mg)	22.5 mL (900 mg)	200 mg/5 mL
15 mL (1200 mg)	30 mL (1200 mg)	200 mg/5 mL

Shake well before each use. Oversized bottle provides shake space. Keep tightly closed.

After mixing, store suspension at 5 deg. to 30 deg. C (41 deg. to 86 deg. F) and use within 10 days. Discard after full dosing is completed.

HOW SUPPLIED

ZITHROMAX 250 mg tablets are supplied as pink modified capsular shaped, engraved, film-coated tablets containing azithromycin dihydrate equivalent to 250 mg of azithromycin. ZITHROMAX 250 mg tablets are engraved with

"PFIZER" on one side and "306" on the other. These are packaged in bottles and blister cards of 6 tablets (Z-PAKS[(R)]) as follows:

Bottles of 30 NDC 0069-3060-30

Boxes of 3 (Z-PAKS[(R)] of 6) NDC 0069-3060-75

Unit Dose package of 50 NDC 0069-3060-86

ZITHROMAX 500 mg tablets are supplied as pink modified capsular shaped, engraved, film-coated tablets containing azithromycin dihydrate equivalent to 500 mg of azithromycin. ZITHROMAX 500 mg tablets are engraved with "Pfizer" on one side and "ZTM500" on the other. These are packaged in bottles and blister cards of 3 tablets (TRI-PAKS(TM)) as follows:

Bottles of 30 NDC 0069-3070-30

Boxes of 3 (TRI-PAKS(TM) of 3 tablets) NDC 0069-3070-75

Unit Dose package of 50 NDC 0069-3070-86

ZITHROMAX tablets should be stored between 15 deg. to 30 deg. C (59 deg. to 86 deg. F).

ZITHROMAX for oral suspension after constitution contains a flavored suspension. ZITHROMAX[(R)] for oral suspension is supplied to provide 100 mg/5 mL or 200 mg/5 mL suspension in bottles as follows:

Azithromycin contents per bottle	NDC
300 mg	0069-3110-19
600 mg	0069-3120-19
900 mg	0069-3130-19
1200 mg	0069-3140-19

See DOSAGE AND ADMINISTRATION for constitution instructions with each bottle type.

Storage: Store dry powder below 30 deg. C (86 deg. F). Store constituted suspension between 5 deg. to 30 deg. C (41 deg. to 86 deg. F) and discard when full dosing is completed.

CLINICAL STUDIES (See INDICATIONS AND USAGE and Pediatric Use .)

Pediatric Patients

From the perspective of evaluating pediatric clinical trials, Days 11-14 were considered on-therapy evaluations because of the extended half-life of azithromycin. Day 11-14 data are provided for clinical guidance. Day 24-32 evaluations were considered the primary test of cure endpoint.

Acute Otitis Media

Safety and efficacy using azithromycin 30 mg/kg given over 5 days

Protocol 1

In a double-blind, controlled clinical study of acute otitis media performed in the United States, azithromycin (10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5) was compared to amoxicillin/clavulanate potassium (4:1). For the 553 patients who were evaluated for clinical efficacy, the clinical success rate (i.e., cure plus improvement) at the Day 11 visit was 88% for azithromycin and 88% for the control agent. For the 521 patients who were evaluated at the Day 30 visit, the clinical success rate was 73% for azithromycin and 71% for the control agent.

In the safety analysis of the above study, the incidence of treatment-related adverse events, primarily gastrointestinal, in all patients treated was 9% with azithromycin and 31% with the control agent. The most common side effects were diarrhea/loose stools (4% azithromycin vs. 20% control), vomiting (2% azithromycin vs. 7% control), and abdominal pain (2% azithromycin vs. 5% control).

Protocol 2

In a non-comparative clinical and microbiologic trial performed in the United States, where significant rates of beta-lactamase producing organisms (35%) were found, 131 patients were evaluable for clinical efficacy. The combined clinical success rate (i.e., cure and improvement) at the Day 11 visit was 84% for azithromycin. For the 122 patients who were evaluated at the Day 30 visit, the clinical success rate was 70% for azithromycin.

Microbiologic determinations were made at the pre-treatment visit. Microbiology was not reassessed at later visits. The following presumptive bacterial/clinical cure outcomes (i.e., clinical success) were obtained from the evaluable group:

Presumed Bacteriologic Eradication

	Day 11 Azithromycin	Day 30 Azithromycin
S. pneumoniae	61/74 (82%)	40/56 (71%)
H. influenzae	43/54 (80%)	30/47 (64%)
M. catarrhalis	28/35 (80%)	19/26 (73%)
S. pyogenes	11/11 (100%)	7/7
Overall	177/217 (82%)	97/137 (73%)

In the safety analysis of this study, the incidence of treatment-related adverse events, primarily gastrointestinal, in all patients treated was 9%. The most common side effect was diarrhea (4%).

Protocol 3

In another controlled comparative clinical and microbiologic study of otitis media performed in the United States, azithromycin was compared to amoxicillin/clavulanate potassium (4:1). This study utilized two of the same investigators as Protocol 2 (above), and these two investigators enrolled 90% of the patients in Protocol 3. For this reason, Protocol 3 was not considered to be an independent study. Significant rates of beta-lactamase producing organisms (20%) were found. Ninety-two (92) patients were evaluable for clinical and microbiologic efficacy. The combined clinical success rate (i.e., cure and improvement) of those patients with a baseline pathogen at the Day 11 visit was 88% for azithromycin vs. 100% for control; at the Day 30 visit, the clinical success rate was 82% for azithromycin vs. 80% for control.

Microbiologic determinations were made at the pre-treatment visit. Microbiology was not reassessed at later visits. At the Day 11 and Day 30 visits, the following presumptive bacterial/clinical cure outcomes (i.e., clinical success) were obtained from the evaluable group:

Presumed Bacteriologic Eradication

	Day 11		Day 30	
	Azithromycin	Control	Azithromycin	Control
S. pneumoniae	25/29 (86%)	26/26 (100%)	22/28 (79%)	18/22 (82%)
H. influenzae	9/11 (82%)	9/9	8/10 (80%)	6/8
M. catarrhalis	7/7	5/5	5/5	2/3
S. pyogenes	2/2	5/5	2/2	4/4
Overall	43/49 (88%)	45/45 (100%)	37/45 (82%)	30/37 (81%)

In the safety analysis of the above study, the incidence of treatment-related adverse events, primarily gastrointestinal, in all patients treated was 4% with azithromycin and 31% with the control agent. The most common side effect was diarrhea/loose stools (2% azithromycin vs. 29% control).

Safety and efficacy using azithromycin 30 mg/kg given over 3 days

Protocol 4

In a double-blind, controlled, randomized clinical study of acute otitis media in pediatric patients from 6 months to 12 years of age, azithromycin (10 mg/kg per day for 3 days) was compared to amoxicillin/clavulanate potassium (7:1) in divided doses q12h for 10 days. Each patient received active drug and placebo matched for the comparator.

For the 366 patients who were evaluated for clinical efficacy at the Day 12 visit, the clinical success rate (i.e., cure plus improvement) was 83% for azithromycin and 88% for the control agent. For the 362 patients who were evaluated at the Day 24-28 visit, the clinical success rate was 74% for azithromycin and 69% for the control agent.

In the safety analysis of the above study, the incidence of treatment-related adverse events, primarily gastrointestinal, in all patients treated was 10.6% with azithromycin and 20.0% with the control agent. The most common side effects were diarrhea/loose stools (5.9% azithromycin vs. 14.6% control), vomiting (2.1% azithromycin vs. 1.1% control), and rash (0.0% azithromycin vs. 4.3% control).

Safety and efficacy using azithromycin 30 mg/kg given as a single dose

Protocol 5

A double blind, controlled, randomized trial was performed at nine clinical centers. Pediatric patients from 6 months to 12 years of age were randomized 1:1 to treatment with either azithromycin (given at 30 mg/kg as a single dose on Day 1) or amoxicillin/clavulanate potassium (7:1), divided q12h for 10 days. Each child received active drug, and placebo matched for the comparator.

Clinical response (Cure, Improvement, Failure) was evaluated at End of Therapy (Day 12-16) and Test of Cure (Day 28-32). Safety was evaluated throughout the trial for all treated subjects. For the 321 subjects who were evaluated at End of Treatment, the clinical success rate (cure plus improvement) was 87% for azithromycin, and 88% for the comparator. For the 305 subjects who were evaluated at Test of Cure, the clinical success rate was 75% for both azithromycin and the comparator.

In the safety analysis, the incidence of treatment-related adverse events, primarily gastrointestinal, was 16.8% with azithromycin, and 22.5% with the comparator. The most common side effects were diarrhea (6.4% with azithromycin vs. 12.7% with the comparator), vomiting (4% with each agent), rash (1.7% with azithromycin vs. 5.2% with the comparator) and nausea (1.7% with azithromycin vs. 1.2% with the comparator).

Protocol 6

In a non-comparative clinical and microbiological trial, 248 patients from 6 months to 12 years of age with documented acute otitis media were dosed with a single oral dose of azithromycin (30 mg/kg on Day 1).

For the 240 patients who were evaluable for clinical modified Intent-to-Treat (MITT) analysis, the clinical success rate (i.e., cure plus improvement) at Day 10 was 89% and for the 242 patients evaluable at Day 24–28, the clinical success rate (cure) was 85%.

Presumed Bacteriologic Eradication

	Day 10	Day 24–28
S. pneumoniae	70/76 (92%)	67/76 (88%)
H. influenzae	30/42 (71%)	28/44 (64%)
M. catarrhalis	10/10 (100%)	10/10 (100%)
Overall	110/128 (86%)	105/130 (81%)

In the safety analysis of this study, the incidence of treatment-related adverse events, primarily gastrointestinal, in all the subjects treated was 12.1%. The most common side effects were vomiting (5.6%), diarrhea (3.2%), and abdominal pain (1.6%).

Pharyngitis/Tonsillitis

In three double-blind controlled studies, conducted in the United States, azithromycin (12 mg/kg once a day for 5 days) was compared to penicillin V (250 mg three times a day for 10 days) in the treatment of pharyngitis due to documented Group A (beta)-hemolytic streptococci (GABHS or *S. pyogenes*). Azithromycin was clinically and microbiologically statistically superior to penicillin at Day 14 and Day 30 with the following clinical success (i.e., cure and improvement) and bacteriologic efficacy rates (for the combined evaluable patient with documented GABHS):

Three U.S. Streptococcal Pharyngitis Studies
Azithromycin vs. Penicillin V EFFICACY
RESULTS

	Day 14	Day 30
Bacteriologic Eradication:		
Azithromycin	323/340 (95%)	255/330 (77%)
Penicillin V	242/332 (73%)	206/325 (63%)
Clinical Success (Cure plus improvement):		
Azithromycin	336/343 (98%)	310/330 (94%)
Penicillin V	284/338 (84%)	241/325 (74%)

Approximately 1% of azithromycin-susceptible *S. pyogenes* isolates were resistant to azithromycin following therapy.

The incidence of treatment-related adverse events, primarily gastrointestinal, in all patients treated was 18% on azithromycin and 13% on penicillin. The most common side effects were diarrhea/loose stools (6% azithromycin vs. 2% penicillin), vomiting (6% azithromycin vs. 4% penicillin), and abdominal pain (3% azithromycin vs. 1% penicillin).

Adult Patients

Acute Bacterial Exacerbations of Chronic Obstructive Pulmonary Disease

In a randomized, double-blind controlled clinical trial of acute exacerbation of chronic bronchitis (AECB), azithromycin (500 mg once daily for 3 days) was compared with clarithromycin (500 mg twice daily for 10 days). The primary endpoint of this trial was the clinical cure rate at Day 21-24. For the 304 patients analyzed in the modified intent to treat analysis at the Day 21-24 visit, the clinical cure rate for 3 days of azithromycin was 85% (125/147) compared to 82% (129/157) for 10 days of clarithromycin.

The following outcomes were the clinical cure rates at the Day 21-24 visit for the bacteriologically evaluable patients by pathogen:

Pathogen	Azithromycin (3 Days)	Clarithromycin (10 Days)
S. pneumoniae	29/32 (91%)	21/27 (78%)
H. influenzae	12/14 (86%)	14/16 (88%)
M. catarrhalis	11/12 (92%)	12/15 (80%)

In the safety analysis of this study, the incidence of treatment-related adverse events, primarily gastrointestinal, were comparable between treatment arms (25% with azithromycin and 29% with clarithromycin). The most common side effects were diarrhea, nausea and abdominal pain with comparable incidence rates for each symptom of 5-9% between the two treatment arms. (See ADVERSE REACTIONS .)

Acute Bacterial Sinusitis

In a randomized, double blind, double-dummy controlled clinical trial of acute bacterial sinusitis, azithromycin (500 mg once daily for 3 days) was compared with amoxicillin/clavulanate (500/125 mg tid for 10 days). Clinical response assessments were made at Day 10 and Day 28. The primary endpoint of this trial was prospectively defined as the clinical cure rate at Day 28. For the 594 patients analyzed in the modified intent to treat analysis at the Day 10 visit, the clinical cure rate for 3 days azithromycin was 88% (268/303) compared to 85% (248/291) for 10 days of amoxicillin/clavulanate. For the 586 patients analyzed in the modified intent to treat analysis at the Day 28 visit, the clinical cure rate for 3 days of azithromycin was 71.5% (213/298) compared to 71.5% (206/288), with a 97.5% confidence interval of-8.4 to 8.3, for 10 days of amoxicillin/clavulanate.

In the safety analysis of this study, the overall incidence of treatment-related adverse events, primarily gastrointestinal, was lower in the azithromycin treatment arm (31%) than in the amoxicillin/clavulanate arm (51%). The most common side effects were diarrhea (17% in the azithromycin arm vs. 32% in the amoxicillin/clavulanate arm), and nausea (7% in the azithromycin arm vs. 12% in the amoxicillin/clavulanate arm). (See ADVERSE REACTIONS).

In an open label, noncomparative study requiring baseline transantral sinus punctures the following outcomes were the clinical success rates at the Day 7 and Day 28 visits for the modified intent to treat patients administered 500 mg of azithromycin once daily for 3 days with the following pathogens:

Pathogen	Azithromycin (500 mg per day for 3 Days)	
	Day 7	Day 28
S. pneumoniae	23/26 (88%)	21/25 (84%)
H. influenzae	28/32 (87%)	24/32 (75%)
M. catarrhalis	14/15 (93%)	13/15 (87%)

The overall incidence of treatment-related adverse events in the noncomparative study was 21% in modified intent to treat patients treated with azithromycin at 500 mg once daily for 3 days with the most common side effects being diarrhea (9%), abdominal pain (4%) and nausea (3%). (See ADVERSE REACTIONS).

ANIMAL TOXICOLOGY

Phospholipidosis (intracellular phospholipid accumulation) has been observed in some tissues of mice, rats, and dogs given multiple doses of azithromycin. It has been demonstrated in numerous organ systems (e.g., eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and pancreas) in dogs treated with azithromycin at doses which, expressed on the basis of mg/m[2] , are approximately equal to the recommended adult human dose, and in rats treated at doses approximately one-sixth of the recommended adult human dose. This effect has been shown to be reversible after cessation of azithromycin treatment. Phospholipidosis has been observed to a similar extent in the tissues of neonatal rats and dogs given daily doses of azithromycin ranging from 10 days to 30 days. Based on the pharmacokinetic data, phospholipidosis has been seen in the rat (30 mg/kg dose) at observed C[max] value of 1.3 micro g/mL (six times greater than the observed C[max] of 0.216 micro g/mL at the pediatric dose of 10 mg/kg). Similarly, it has been shown in the dog (10 mg/kg dose) at observed C[max] value of 1.5 micro g/mL (seven times greater than the observed same C[max] and drug dose in the studied pediatric population). On a mg/m[2] basis, 30 mg/kg dose in the neonatal rat (135 mg/m[2]) and 10 mg/kg dose in the neonatal dog (79 mg/m[2]) are approximately 0.5 and 0.3 times, respectively, the recommended dose in the pediatric patients with an average body weight of 25 kg. Phospholipidosis, similar to that seen in the adult animals, is reversible after cessation of azithromycin treatment. The significance of these findings for animals and for humans is unknown.

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Legal Entity Type: Corporation
State or Country of Incorporation: Belgium

GOODS AND/OR SERVICES

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Class Status: Active

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2002-02-05 - Registered - Principal Register

2001-11-13 - Published for opposition

2001-10-24 - Notice of publication

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2001-05-29 - Approved for Pub - Principal Register (Initial exam)

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191 of 192 DOCUMENTS

Physician's Desk Reference for Prescription Drugs

Zyrtec-D 12 Hour Extended Release Tablets(Pfizer)

BODY:

DESCRIPTION

ZYRTEC-D 12 HOUR(TM) (cetirizine hydrochloride 5 mg and pseudoephedrine hydrochloride 120 mg) Extended Release Tablets for oral administration contain 5 mg of cetirizine hydrochloride for immediate release and 120 mg of pseudoephedrine hydrochloride for extended release in a bilayer tablet. Tablets also contain as inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose.

Cetirizine hydrochloride, one of the two active components of ZYRTEC-D 12 HOUR Extended Release Tablets, is an orally active and selective H[1]-receptor antagonist. The chemical name is (+/-)-2-4-(4-chlorophenyl)phenylmethyl-1-piperazinyl ethoxy acetic acid, dihydrochloride. Cetirizine hydrochloride is a racemic compound with an empirical formula of C[21] H[25] ClN[2] O[3] *2HCl. The molecular weight is 461.82. Cetirizine hydrochloride is a white, crystalline powder and is water-soluble. The chemical structure is shown below:

See Image

Pseudoephedrine hydrochloride, the other active ingredient of ZYRTEC-D 12 HOUR Extended Release Tablets, is an adrenergic (vasoconstrictor) agent with the chemical name (1S.2S)-2-methylamino-1-phenyl-1-propanol hydrochloride. The molecular weight is 201.70. The molecular formula is C[10] H[15] NO*HCl. Pseudoephedrine hydrochloride occurs as fine, white to off-white crystals or powder, having a faint characteristic odor. It is very soluble in water, freely soluble in alcohol, and sparingly soluble in chloroform. The chemical structure is shown below:

See Image

CLINICAL PHARMACOLOGY

Mechanisms of Action: Cetirizine, a metabolite of hydroxyzine, is an antihistamine; its principal effects are mediated via selective inhibition of H[1] receptors. The antihistaminic activity of cetirizine has been clearly documented in a variety of animal and human models. *In vivo* and *Ex vivo* animal models have shown negligible anticholinergic and antiserotonergic activity. In clinical trials, however, dry mouth was more common with cetirizine than with placebo. *In vitro* receptor binding studies have shown no measurable affinity for other than H[1] receptors. Autoradiographic studies with radiolabeled cetirizine in the rat have shown negligible penetration into the brain. *Ex vivo* experiments in the mouse have shown that systemically administered cetiri-zine does not significantly occupy cerebral H[1] receptors.

Pseudoephedrine hydrochloride is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa. Pseudoephedrine hydrochloride is recognized as an effective agent for the relief of nasal congestion due to allergic rhinitis. Pseudoephedrine produces peripheral effects similar to those of ephedrine and central effects similar to, but less intense than, amphetamines. It has the potential for excitatory side effects.

Pharmacokinetics:

Absorption: The bioavailability of cetirizine hydrochloride and pseudoephedrine hydrochloride from ZYRTEC-D 12 HOUR Extended Release Tablets is not significantly different from that achieved with separate administration of a cetirizine 5 mg tablet and a pseudoephedrine 120 mg extended release caplet. Co-administration of cetirizine and

pseudoephedrine does not significantly affect the bioavailability of either component.

Following a single dose of the ZYRTEC-D 12 HOUR Extended Release Tablet, a mean peak plasma concentration (Cmax) of 114 ng/mL at a time (Tmax) of 2.2 hours postdose was observed for cetirizine and a mean Cmax of 309 ng/mL at a Tmax of 4.4 hours postdose was observed for pseudoephedrine.

When healthy volunteers were administered multiple doses of the ZYRTEC-D 12 HOUR Extended Release Tablet to reach steady-state concentrations (cetirizine hydrochloride 5 mg and pseudoephedrine hydrochloride 120 mg twice daily for seven days), a mean Cmax of 178 ng/mL was observed for cetirizine and 526 ng/mL for pseudoephedrine.

Food had no significant effect on the extent of cetirizine absorption (AUC), but Tmax was delayed by 1.8 hours and Cmax was decreased by 30%. Food had no significant effect on the pharmacokinetics of pseudoephedrine. ZYRTEC-D 12 HOUR Extended Release Tablets may be given with or without food (see DOSAGE AND ADMINISTRATION).

Distribution: The mean plasma protein binding of cetiri-zine is 93%, independent of concentration in the range of 25-1000 ng/mL, which includes the therapeutic plasma levels observed. The apparent volume of distribution (V/F) of pseudoephedrine has been reported to be 2.6-3.3 L/kg. No plasma protein binding data in humans are available.

Metabolism: A human mass balance study of cetirizine in 6 healthy male volunteers indicated that 70% of the administered radioactivity was recovered in the urine and 10% in the feces. Approximately 50% of the radioactivity was identified in the urine as unchanged drug. Most of the rapid increase in peak plasma radioactivity was associated with parent drug, suggesting low first pass metabolism. Cetiri-zine is metabolized to a limited extent by oxidative O-dealkylation to a metabolite with negligible antihistaminic activity. The enzyme or enzymes responsible for this metabolism have not been identified.

One to seven percent of the pseudoephedrine dose appeared to be metabolized to norpseudoephedrine by N-demethylation after a single dose.

Elimination: After administration of the ZYRTEC-D 12 HOUR Extended Release Tablet, the mean elimination half-life of cetirizine was 7.9 hours and the mean elimination half-life of pseudoephedrine was 6.0 hours.

It was reported that 0.4-0.7% of the pseudoephedrine dose was estimated to be excreted in the breast milk over 24 hours after a single dose. The pattern of the relative milk/plasma drug concentration profile showed that pseudo-ephedrine concentrations in milk were 2-to 3-fold higher than those in plasma.

Drug Interactions

Pharmacokinetic interaction trials with cetirizine in adults were conducted with pseudoephedrine, antipyrine, ketoconazole, erythromycin and azithromycin. No interactions were observed. In a multiple dose study of theophylline (400 mg once daily for 3 days) and cetirizine (20 mg once daily for 3 days), a 16% decrease in the clearance of cetiri-zine was observed. The disposition of theophylline was not altered by concomitant cetirizine administration.

Special Populations

Pediatrics: Although cetirizine pharmacokinetics have been studied in children, ZYRTEC-D 12 HOUR Extended Release Tablets contain 120 mg of pseudoephedrine hydrochloride, which exceeds the recommended dose for patients less than 12 years of age. Therefore, ZYRTEC-D 12 HOUR Extended Release Tablets are not recommended for patients under 12 years of age.

Geriatrics: Following a single, 10-mg oral dose of cetiri-zine, the elimination half-life was prolonged by 50% and the apparent total body clearance was 40% lower in 16 geriatric subjects with a mean age of 77 years compared to 14 adult subjects with a mean age of 53 years. The decrease in cetirizine clearance in these elderly volunteers may be related to decreased renal function.

The pharmacokinetics of pseudoephedrine has not been adequately studied in geriatric subjects.

Gender: The effect of gender on cetirizine or pseudoephedrine pharmacokinetics has not been adequately studied.

Race: The effect of race on cetirizine or pseudoephedrine pharmacokinetics has not been adequately studied.

Renal Impairment: The kinetics of cetirizine were studied following multiple, oral, 10-mg daily doses of cetirizine for 7 days in 7 normal volunteers (creatinine clearance 89-128 mL/min), 8 patients with mild renal function impairment (creatinine clearance 42-77 mL/min) and 7 patients with moderate renal function impairment (creatinine clearance 11-31 mL/min). The pharmacokinetics of cetirizine were similar in patients with mild impairment and normal volunteers. Moderately impaired patients had a 3-fold increase in half-life and a 70% decrease in clearance compared to normal volunteers.

Patients on hemodialysis (n=5) given a single, 10-mg dose of cetirizine had a 3-fold increase in half-life and a 70% decrease in clearance compared to normal volunteers. Less than 10% of the administered dose was removed during the single dialysis session.

About 55-75% of an administered dose of pseudoephedrine hydrochloride is excreted unchanged in the urine; the remainder is apparently metabolized in the liver. Therefore, pseudoephedrine may accumulate in patients with renal insufficiency.

Dosing adjustment is necessary in patients with moderate or severe renal impairment and in patients on dialysis (see DOSAGE AND ADMINISTRATION).

Hepatic Impairment: Sixteen patients with chronic liver diseases (hepatocellular, cholestatic, and biliary cirrhosis), given 10 or 20 mg of cetirizine as a single, oral dose had a 50% increase in half-life along with a corresponding 40% decrease in clearance compared to 16 healthy subjects.

The effect of hepatic impairment on pseudoephedrine pharmacokinetics is unknown.

Dosing adjustment may be necessary in patients with hepatic impairment (see DOSAGE AND ADMINISTRATION).

Pharmacodynamics: Trials in 69 adult normal volunteers (aged 20-61 years) showed that cetirizine at doses of 5 and 10 mg inhibited the skin wheal and flare caused by the intradermal injection of histamine. The onset of this activity after a single 10-mg dose occurred within 20 minutes in 50% of subjects and within one hour in 95% of subjects; this activity persisted for at least 24 hours. The effects of intradermal injection of various other mediators or histamine releasers were also inhibited by cetirizine. In mildly asthmatic subjects, cetirizine at 5 to 20 mg blocked bronchoconstriction due to nebulized histamine, with virtually total blockade after a 20 mg dose. In trials conducted for up to 12 hours following cutaneous antigen challenge, the late phase recruitment of eosinophils, neutrophils and basophils, components of the allergic inflammatory response, was inhibited by cetirizine at a dose of 20 mg. The clinical significance of these findings is not known.

In four clinical trials in healthy adult males, no clinically significant mean increases in QTc were observed in cetirizine treated subjects. In the first study, a placebo-controlled crossover trial, cetirizine was given at doses up to 60 mg per day, 6 times the maximum clinical dose, for 1 week, and no significant mean QTc prolongation occurred. In the second study, a crossover trial, cetirizine 20 mg and erythromycin (500 mg every 8 hours) were given alone and in combination. There was no significant effect on QTc with the combination or with cetirizine alone. In the third trial, also a crossover study, cetirizine 20 mg and ketoconazole (400 mg per day) were given alone and in combination. Cetirizine caused a mean increase in QTc of 9.1 msec from baseline after 10 days of therapy. Ketoconazole also increased QTc by 8.3 msec. The combination caused an increase of 17.4 msec, equal to the sum of the individual effects. Thus, there was no significant drug interaction on QTc with the combination of cetirizine and ketoconazole. In the fourth study, a placebo-controlled parallel trial, cetirizine 20 mg was given alone or in combination with

azithromycin (500 mg as a single dose on the first day followed by 250 mg once daily). There was no significant increase in QTc with cetirizine 20 mg alone or in combination with azithromycin.

In a six-week, placebo-controlled study of 186 patients (aged 12-64 years) with allergic rhinitis and mild to moderate asthma, cetirizine 10 mg once daily improved rhinitis symptoms and did not alter pulmonary function. This study supports the safety of administering cetirizine to allergic rhinitis patients with mild to moderate asthma.

Clinical Trials:

ZYRTEC-D 12 HOUR Extended Release Tablets: Two multicenter, randomized, double-blind, placebo-controlled clinical trials (n = 1094 and n = 1000) comparing ZYRTEC-D 12 HOUR Extended Release Tablets (cetirizine hydrochloride 5 mg and pseudoephedrine hydrochloride 120 mg) to active control and placebo for two weeks in patients 12 years and older with seasonal allergic rhinitis were conducted in the United States. In the two trials, 390 patients were aged 12 to 17 years. The primary efficacy measure in both trials was the mean change from baseline in the subject-rated Total Symptom Severity Complex (TSSC) score, which included the following symptoms: sneezing, runny nose, itchy nose, itchy eyes, watery eyes, postnasal drip, and nasal congestion. In both trials patients who received ZYRTEC-D showed a significant reduction in the TSSC score compared to those who received placebo.

Zyrtec Tablets: Nine multicenter, randomized, double-blind, clinical trials comparing cetirizine 5 to 20 mg to placebo in patients 12 years and older with seasonal or perennial allergic rhinitis were conducted in the United States. Five of these showed significant reductions in symptoms of allergic rhinitis, 3 in seasonal allergic rhinitis (1 to 4 weeks in duration) and 2 in perennial allergic rhinitis for up to 8 weeks in duration. In general, the 10 mg dose was more effective than the 5 mg dose and the 20 mg dose gave no added effect. Some of these trials included pediatric patients aged 12 to 16 years.

INDICATIONS AND USAGE

ZYRTEC-D 12 HOUR Extended Release Tablets should be administered when both the antihistaminic properties of cetirizine hydrochloride and the nasal decongestant properties of pseudoephedrine hydrochloride are desired.

ZYRTEC-D 12 HOUR Extended Release Tablets are indicated for the relief of nasal and non-nasal symptoms associated with seasonal or perennial allergic rhinitis in adults and children 12 years of age and older.

CONTRAINDICATIONS

ZYRTEC-D 12 HOUR Extended Release Tablets are contraindicated in patients with a known hypersensitivity to any of its ingredients or to hydroxyzine.

Due to its pseudoephedrine component, ZYRTEC-D 12 HOUR Extended Release Tablets are contraindicated in patients with narrow-angle glaucoma or urinary retention, and in patients receiving monoamine oxidase (MAO) inhibitor therapy or within fourteen (14) days of stopping such treatment (see PRECAUTIONS , Drug Interactions section). It is also contraindicated in patients with severe hypertension, or severe coronary artery disease, and in those who have shown hypersensitivity or idiosyncrasy to its components, to adrenergic agents, or to other drugs of similar chemical structures. Manifestations of patient idiosyncrasy to adrenergic agents include insomnia, dizziness, weakness, tremor, or arrhythmias.

WARNINGS

Sympathomimetic amines should be used judiciously and sparingly in patients with hypertension, diabetes mellitus, ischemic heart disease, increased intraocular pressure, hyperthyroidism, renal impairment, or prostatic hypertrophy (see CONTRAINDICATIONS). Sympathomimetic amines may produce central nervous system stimulation with convulsions or cardiovascular collapse with accompanying hypotension. The elderly are more likely to have adverse reactions to sympathomimetic amines.

PRECAUTIONS

Due to its pseudoephedrine component, ZYRTEC-D 12 HOUR Extended Release Tablets should be used with caution in patients with hypertension, diabetes mellitus, ischemic heart disease, increased intraocular pressure, hyperthyroidism, renal impairment, or prostatic hypertrophy (see WARNINGS and CONTRAINDICATIONS). Patients with decreased renal function should be given a lower initial dose (one tablet per day) because they have reduced elimination of cetirizine and pseudoephedrine (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Activities Requiring Mental Alertness: In clinical trials, the occurrence of somnolence has been reported in some patients taking cetirizine or ZYRTEC-D 12 HOUR Extended Release Tablets; due caution should therefore be exercised when driving a car or operating potentially dangerous machinery after taking ZYRTEC-D 12 HOUR Extended Release Tablets. Concurrent use of ZYRTEC-D 12 HOUR Extended Release Tablets with alcohol or other CNS depressants should be avoided because additional reductions in alertness and additional impairment of CNS performance may occur.

Drug Interactions: Cetirizine hydrochloride and pseudo-ephedrine hydrochloride do not influence the pharmacokinetics of each other when administered concomitantly.

No clinically significant drug interactions have been found with cetirizine and theophylline at a low dose, azithromycin, ketoconazole, or erythromycin. There was a small decrease in the clearance of cetirizine caused by a 400 mg dose of theophylline; it is possible that larger theophylline doses could have a greater effect.

Due to the pseudoephedrine component, ZYRTEC-D 12 HOUR Extended Release Tablets are contraindicated in patients taking monoamine oxidase (MAO) inhibitors and for 14 days after stopping use of an MAO inhibitor. Concomitant use with antihypertensive drugs that interfere with sympathetic activity (e.g., methyldopa, mecamylamine, and reserpine) may reduce their antihypertensive effects. Increased ectopic pacemaker activity can occur when pseudoephedrine is used concomitantly with digitalis. Care should be taken in the administration of ZYRTEC-D 12 HOUR Extended Release Tablets concomitantly with other sympathomimetic amines because combined effects on the cardiovascular system may be harmful to the patient (see WARNINGS).

Carcinogenesis, Mutagenesis and Impairment of Fertility: There are no carcinogenicity trials of pseudoephedrine and cetirizine in combination.

Cetirizine: In a 2-year study in rats, cetirizine was not carcinogenic at dietary doses up to 20 mg/kg (approximately 15 times the maximum recommended daily dose in adults on a mg/m[2] basis). In a 2-year study in mice, cetirizine caused an increased incidence of benign liver tumors in males at a dietary dose of 16 mg/kg (approximately 6 times the maximum recommended daily dose in adults on a mg/m[2] basis). No increase in the incidence of liver tumors was observed in mice at a dietary dose of 4 mg/kg (approximately 2 times the maximum recommended daily dose in adults on a mg/m[2] basis). The clinical significance of these findings during long-term use of ZYRTEC-D 12 HOUR Extended Release Tablets is not known.

Pseudoephedrine: Two-year studies in rats and mice conducted under the auspices of the National Toxicology Program (NTP) demonstrated no evidence of carcinogenic potential with ephedrine sulfate, a structurally related drug with pharmacological properties similar to pseudoephedrine, at dietary doses up to 10 and 27 mg/kg, respectively (approximately 1/3 and 1/2, respectively, the maximum recommended daily dose of pseudoephedrine in adults on a mg/m[2] basis).

Cetirizine was not mutagenic in the Ames test or mouse lymphoma test and not clastogenic in the human lymphocyte assay or the *in vivo* rodent micronucleus test. Likewise, the combination of cetirizine and pseudoephedrine in a 1:24 ratio was not mutagenic or clastogenic in these tests. However, the Ames and mouse lymphoma assays did not strictly adhere to test standards.

In a reproductive toxicity study in rats, combination oral doses of cetirizine and pseudoephedrine up to 6/154 mg/kg (approximately 5 times the maximum recommended daily dose in adults on a mg/m[2] basis) had no effect on fertility.

Pregnancy Category C: In rats, the combination of cetiri-zine and pseudoephedrine caused developmental toxicity when administered orally at 6/154 mg/kg (approximately 5 times the maximum recommended daily dose in adults on a mg/m[2] basis). When rats were dosed throughout pregnancy with oral doses of cetirizine/pseudoephedrine, 6/154 mg/kg increased the number of fetal skeletal malformations (rib distortions) and variants (unossified sternebrae). When dosing was continued through lactation, 6/154 mg/kg also decreased the viability and weight gain of offspring. These effects were not observed at 1.6/38 mg/kg (approximately equivalent to the maximum recommended daily dose in adults on a mg/m[2] basis). No embryofetal toxicity was observed when rabbits were dosed throughout organogenesis with oral doses of cetirizine/pseudoephedrine of up to 6/154 mg/kg (approximately 10 times the maximum recommended daily dose in adults on a mg/m[2] basis). Because there are no adequate and well-controlled trials in pregnant women, ZYRTEC-D 12 HOUR Extended Release Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: In rats the combination of cetirizine/pseudoephedrine decreased the viability and weight gain of offspring when administered orally to dams throughout pregnancy and lactation at 6/154 mg/kg (approximately 5 times the maximum recommended daily dose in adults on a mg/m[2] basis). This effect was not observed at 1.6/38 mg/kg (approximately equivalent to the maximum recommended daily dose in adults on a mg/m[2] basis). For cetirizine administered alone, studies in dogs indicate that approximately 3% of the dose is excreted in milk, and cetirizine has been reported to be excreted in human breast milk. For pseudoephedrine administered alone, 0.4-0.7% of the dose has been reported to be excreted in human breast milk.

Because cetirizine and pseudoephedrine are excreted in milk, use of ZYRTEC-D 12 HOUR Extended Release Tablets in nursing mothers is not recommended.

Geriatric Use: Clinical trials of ZYRTEC-D 12 HOUR Extended Release Tablets did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, although the elderly are more likely to have adverse reactions to sympathomimetic amines. In general, dosing in an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

The cetirizine and pseudoephedrine components of ZYRTEC-D 12 HOUR Extended Release Tablets are known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see CLINICAL PHARMACOLOGY).

Cetirizine: Of the total number of subjects in clinical trials of cetirizine alone, 186 were 65 years and over, while 39 were 75 years and over. No overall differences in safety were observed between these subjects and younger subjects, and other reported experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. With regard to efficacy, clinical trials of cetirizine for each approved indication did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently than younger patients.

Pediatric Use: ZYRTEC-D 12 HOUR Extended Release Tablets contain 120 mg of pseudoephedrine hydrochloride in an extended release formulation. This dose of pseudoephedrine exceeds the recommended dose for pediatric patients under 12 years of age. Therefore, clinical trials of ZYRTEC-D 12 HOUR Extended Release Tablets have not been conducted in patients under 12 years of age.

ADVERSE REACTIONS

ZYRTEC-D 12 HOUR Extended Release Tablets

In two double-blind, placebo-controlled trials (n = 2094) in which 701 patients with seasonal allergic rhinitis were treated with ZYRTEC-D 12 HOUR Extended Release Tablets (cetirizine hydrochloride 5 mg and pseudoephedrine hydrochloride 120 mg) twice daily for two weeks, the percent of patients who withdrew prematurely due to adverse

events was 2.0% in the ZYRTEC-D group, compared with 1.1% in the placebo group. All adverse events that were reported by greater than 1% of patients in the ZYRTEC-D group are listed in Table 1.

TABLE 1. ADVERSE EXPERIENCES REPORTED IN PATIENTS AGED 12 YEARS AND OLDER IN SEASONAL ALLERGIC RHINITIS TRIALS OF ZYRTEC-D 12 HOUR EXTENDED RELEASE TABLETS AT RATES OF 1% OR GREATER (PERCENT INCIDENCE)

ADVERSE EXPERIENCE	ZYRTEC-D (n = 701)	PLACEBO (n = 696)
Insomnia	4.0	0.6
Dry Mouth	3.6	0.4
Fatigue	2.4	0.9
Somnolence	1.9	0.1
Pharyngitis	1.7	1.1
Epistaxis	1.1	0.9
Accidental Injury	1.1	0.4
Dizziness	1.1	0.1
Sinusitis	1.0	0.6

ZYRTEC Tablets

Controlled and uncontrolled clinical trials of cetirizine conducted in the United States and Canada included more than 6000 patients aged 12 years and older, with more than 3900 receiving cetirizine at doses of 5 to 20 mg per day. The duration of treatment ranged from 1 week to 6 months, with a mean exposure of 30 days.

Most adverse reactions reported during therapy with cetirizine were mild or moderate. In placebo-controlled trials, the incidence of discontinuations due to adverse reactions in patients receiving cetirizine 5 mg or 10 mg was not significantly different from placebo (2.9% vs. 2.4%, respectively).

The most common adverse reaction in patients aged 12 years and older that occurred more frequently on cetirizine than placebo was somnolence. The incidence of somnolence associated with cetirizine was dose related, 6% in placebo, 11% at 5 mg and 14% at 10 mg. Discontinuations due to somnolence for cetirizine were uncommon (1.0% on cetirizine vs. 0.6% on placebo). Fatigue and dry mouth also appeared to be treatment-related adverse reactions. There were no differences by age, race, gender or by body weight with regard to the incidence of adverse reactions.

Table 2 lists adverse experiences in patients aged 12 years and older that were reported for cetirizine 5 and 10 mg in controlled clinical trials in the United States and were more common with cetirizine than placebo.

TABLE 2. ADVERSE EXPERIENCES REPORTED IN PATIENTS AGED 12 YEARS AND OLDER IN PLACEBO-CONTROLLED UNITED STATES CETIRIZINE TRIALS (MAXIMUM DOSE OF 10 MG) AT RATES OF 2% OR GREATER (PERCENT INCIDENCE)

ADVERSE EXPERIENCE	CETIRIZINE (n=2034)	PLACEBO (n=1612)
Somnolence	13.7	6.3
Fatigue	5.9	2.6
Dry Mouth	5.0	2.3
Pharyngitis	2.0	1.9
Dizziness	2.0	1.2

In addition, headache and nausea occurred in more than 2% of the patients, but were more common in placebo patients.

The following events were observed infrequently (less than 2%), in 3982 adults and children 12 years and older or in 659 pediatric (6 to 11 years) patients who received cetirizine in U.S. trials, including an open study of six months duration. A causal relationship of these infrequent events with cetirizine administration has not been established.

Autonomic Nervous System: anorexia, flushing, increased salivation, urinary retention.

Cardiovascular: cardiac failure, hypertension, palpitation, tachycardia.

Central and Peripheral Nervous Systems: abnormal coordination, ataxia, confusion, dysphonia, hyperesthesia, hyperkinesia, hypertonia, hypoesthesia, leg cramps, migraine, myelitis, paralysis, paresthesia, ptosis, syncope, tremor, twitching, vertigo, visual field defect.

Gastrointestinal: abnormal hepatic function, aggravated tooth caries, constipation, dyspepsia, eructation, flatulence, gastritis, hemorrhoids, increased appetite, melena, rectal hemorrhage, stomatitis including ulcerative stomatitis, tongue discoloration, tongue edema.

Genitourinary: cystitis, dysuria, hematuria, micturition frequency, polyuria, urinary incontinence, urinary tract infection.

Hearing and Vestibular: deafness, earache, ototoxicity, tinnitus.

Metabolic/Nutritional: dehydration, diabetes mellitus, thirst.

Musculoskeletal: arthralgia, arthritis, arthrosis, muscle weakness, myalgia.

Psychiatric: abnormal thinking, agitation, amnesia, anxiety, decreased libido, depersonalization, depression, emotional lability, euphoria, impaired concentration, insomnia, nervousness, paroniria, sleep disorder.

Respiratory System: bronchitis, dyspnea, hyperventilation, increased sputum, pneumonia, respiratory disorder, rhinitis, sinusitis, upper respiratory tract infection.

Reproductive: dysmenorrhea, female breast pain, intermenstrual bleeding, leukorrhea, menorrhagia, vaginitis.

Reticuloendothelial: lymphadenopathy.

Skin: acne, alopecia, angioedema, bullous eruption, dermatitis, dry skin, eczema, erythematous rash, furunculosis, hyperkeratosis, hypertrichosis, increased sweating, maculopapular rash, photosensitivity reaction, photosensitivity toxic reaction, pruritus, purpura, rash, seborrhea, skin disorder, skin nodule, urticaria.

Special Senses: parosmia, taste loss, taste perversion.

Vision: blindness, conjunctivitis, eye pain, glaucoma, loss of accommodation, ocular hemorrhage, xerophthalmia.

Body as a Whole: accidental injury, asthenia, back pain, chest pain, enlarged abdomen, face edema, fever, generalized edema, hot flashes, increased weight, leg edema, malaise, nasal polyp, pain, pallor, periorbital edema, peripheral edema, rigors.

Occasional instances of transient, reversible hepatic transaminase elevations have occurred during cetirizine therapy. Hepatitis with significant transaminase elevation and elevated bilirubin in association with the use of cetirizine has been reported.

In foreign marketing experience or experience in the post market period, the following additional rare, but potentially

severe adverse events have been reported: anaphylaxis, cholestasis, glomerulonephritis, hemolytic anemia, hepatitis, orofacial dyskinesia, severe hypotension, stillbirth, thrombocytopenia, aggressive reaction and convulsions.

Pseudoephedrine Hydrochloride

Pseudoephedrine hydrochloride may cause mild CNS stimulation in hypersensitive patients. Nervousness, excitability, restlessness, dizziness, weakness, or insomnia may occur. Headache, nausea, drowsiness, tachycardia, palpitation, pressor activity, and cardiac arrhythmias have been reported. Sympathomimetic drugs have also been associated with other untoward effects such as fear, anxiety, tenseness, tremor, hallucinations, seizures, pallor, respiratory difficulty, dysuria, and cardiovascular collapse.

OVERDOSAGE

Information regarding acute overdosage is limited to experience with cetirizine alone and the marketing history of pseudoephedrine hydrochloride.

Overdosage has been reported with cetirizine. In one adult patient who took 150 mg of cetirizine, the patient was somnolent but did not display any other clinical signs or abnormal blood chemistry or hematology results. In an 18-month-old pediatric patient who took an overdose of cetirizine (approximately 180 mg), restlessness and irritability were observed initially; this was followed by drowsiness. Should overdose occur, treatment should be symptomatic or supportive, taking into account any concomitantly ingested medications. There is no known specific antidote to cetirizine. Cetirizine is not effectively removed by dialysis, and dialysis will be ineffective unless a dialyzable agent has been concomitantly ingested. The acute minimal lethal oral doses in mice and rats were 237 and 562 mg/kg, respectively (approximately 95 and 460 times the maximum recommended daily dose in adults on a mg/m[2] basis). In rodents, the target of acute toxicity was the central nervous system, and the target of multiple-dose toxicity was the liver.

In large doses, sympathomimetics may give rise to giddiness, headache, nausea, vomiting, sweating, thirst, tachycardia, precordial pain, palpitations, difficulty in micturition, muscular weakness and tenseness, anxiety, restlessness, and insomnia. Many patients can present a toxic psychosis with delusions and hallucinations. Some may develop cardiac arrhythmias, circulatory collapse, convulsions, coma and respiratory failure.

DOSAGE AND ADMINISTRATION

Adults and Children 12 Years of Age and Older: The recommended dose of ZYRTEC-D 12 HOUR Extended Release Tablets is one tablet twice daily for adults and children 12 years of age and older. ZYRTEC-D 12 HOUR Extended Release Tablets may be given with or without food.

Dose Adjustment for Renal and Hepatic Impairment: In patients with decreased renal function (creatinine clearance 11-31 mL/min), patients on hemodialysis (creatinine clearance less than 7 mL/min), and in hepatically impaired patients, a dose of one tablet once daily is recommended (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

ZYRTEC-D 12 HOUR Extended Release Tablets should be swallowed whole, and should not be broken or chewed.

HOW SUPPLIED

ZYRTEC-D 12 HOUR(TM) Extended Release Tablets are white, round, biconvex, bilayer tablets containing 5 mg cetirizine hydrochloride in an immediate release layer and 120 mg pseudoephedrine hydrochloride in an extended release layer. ZYRTEC-D 12 HOUR Extended Release Tablets are supplied in high-density polyethylene bottles of 100 tablets fitted with polypropylene child-resistant closures (NDC 0069-1630-66).

ZYRTEC-D 12 HOUR Extended Release Tablets are engraved with ZYRTEC-D on one side.

STORAGE: *Store at 20-25 deg. C (68-77 deg. F); excursions permitted to 15-30 deg. C (59-86 deg. F) see USP*

Controlled Room Temperature

Cetirizine is licensed from UCB Pharma, Inc.

Manufactured/Distributed by

Pfizer Labs

Division of Pfizer Inc, NY, NY 10017

Marketed by

UCB Pharma, Inc.

Smyrna, GA 30080

69-5723-00-3 Revised August 2003

PRODUCT PHOTO(S): NOTE: These photos can be used only for identification by shape, color, and imprint. They do not depict actual *or relative* size.

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See Image

LANGUAGE: ENGLISH

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Serial Number: 71056876 Assignment Information

Registration Number: 83823

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(words only): EX-LAX

Standard Character claim: No

Current Status: This registration has been renewed.

Date of Status: 2002-01-24

Filing Date: 1911-06-07

Transformed into a National Application: No

Registration Date: 1911-10-17

Register: Principal

Law Office Assigned: (NOT AVAILABLE)

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LAST APPLICANT(S)/OWNER(S) OF RECORD

1. NOVARTIS AG

Address:
NOVARTIS AG
CH-4056

BASEL
Switzerland
Legal Entity Type: Corporation
State or Country of Incorporation: Switzerland

GOODS AND/OR SERVICES

U.S. Class: 018 (International Class 005)
Class Status: Active
LAXATIVE PREPARATION
Basis: 1(a)
First Use Date: 1908-05-00
First Use in Commerce Date: 1908-05-00

ADDITIONAL INFORMATION

(NOT AVAILABLE)

MADRID PROTOCOL INFORMATION

(NOT AVAILABLE)

PROSECUTION HISTORY

2003-01-02 - TEAS Change Of Correspondence Received

2002-01-24 - Fifth renewal 10 year

2002-01-24 - Section 8 (10-year) accepted/ Section 9 granted

2001-11-08 - Combined Section 8 (10-year)/Section 9 filed

2001-11-13 - Combined Section 8 (10-year)/Section 9 filed

1991-10-09 - Fourth renewal 10 year

1991-09-19 - Section 9 filed/check record for Section 8

1991-07-16 - Section 8 (6-year) accepted & Section 15 acknowledged

1990-09-14 - Section 8 (6-year) and Section 15 Filed

1971-10-17 - Third renewal

1984-12-11 - Published Section 12(c)

1984-10-25 - Published Section 12(c)

1984-10-16 - Post Registration action correction

1984-02-06 - Section 12(c) affidavit filed

1983-04-05 - Published Section 12(c)

1983-04-05 - Published Section 12(c)

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Domestic Representative
NOVARTIS PHARMACEUTICALS CORPORATION

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Physician's Desk Reference for Non-Prescription Drugs

Ex Lax Regular Strength Pills(Novartis Consumer)

BODY:

Active Ingredients: *Regular Strength Ex Lax Laxative Pills:* Sennosides, USP, 15 mg. *Maximum Relief Formula Ex Lax Laxative Pills:* Sennosides, USP, 25 mg.

Use: For Relief of

OCCASIONAL CONSTIPATION (IRREGULARITY). This product generally produces bowel movement in 6 to 12 hours.

Warnings:

as with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.

Unless directed by a doctor, do not use:

laxative products when abdominal pain, nausea, or vomiting is present.laxative products for a period longer than 1 week.

Consult a doctor before using a laxative if:

you have noticed a sudden change in bowel habits that persists over a period of 2 weeks.

Consult a doctor and stop using a laxative if:

rectal bleeding occurs or you fail to have a bowel movement after use because this may indicate a serious condition.

Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately.

Dosage and Administration: *Regular Strength Ex Lax Laxative Pills, and Maximum Strength Ex Lax Laxative Pills*—Adults and children 12 years of age and over: take 2 pills once or twice daily with a glass of water. Children 6 to under 12 years of age: take 1 pill once or twice daily with a glass of water. Children under 6 years of age: consult a doctor.

Inactive Ingredients: *Regular Strength Ex Lax Laxative Pills*—acacia, alginic acid, carnauba wax, colloidal silicon dioxide, dibasic calcium phosphate, iron oxides, magnesium stearate, microcrystalline cellulose, sodium benzoate, sodium lauryl sulfate, starch, stearic acid, sucrose, talc, titanium dioxide. Sodium-free. *Maximum Strength Ex Lax Laxative Pills:* acacia, alginic acid, FD&C Blue No. 1 aluminum lake, carnauba wax, colloidal silicon dioxide, dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose, povidone, sodium benzoate, sodium lauryl sulfate, starch, stearic acid, sucrose, talc, titanium dioxide. Very low sodium.

Store at controlled room temperature 20–25 deg. C (68–77 deg. F)

How Supplied: *Regular Strength Ex Lax Laxative Pills*—Available in boxes of 8 ct. and 30 ct. pills. *Maximum Strength Ex Lax Laxative Pills*—Available in boxes of 24 ct., 48 ct., and 90 ct. pills.

Novartis Consumer Health, Inc.

Parsippany, NJ 07054-0622 ©2003

PRODUCT PHOTO(S): NOTE: These photos can be used only for identification by shape, color, and imprint. They do not depict actual *or relative* size.

The product samples shown here have been supplied by the manufacturer and reproduced in full color by PDR as a quick-reference identification aid. While every effort has been made to assure accurate reproduction, please remember that any visual identification should be considered preliminary. In cases of poisoning or suspected overdosage, the drug's identity should be verified by chemical analysis.
See Image

LANGUAGE: ENGLISH

LOAD-DATE: February 11, 2005

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This page was generated by the TARR system on 2006-06-28 20:33:29 ET

Serial Number: 73786484 Assignment Information

Registration Number: 1567931

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Standard Character claim: No

Current Status: This registration has been renewed.

Date of Status: 2000-06-30

Filing Date: 1989-03-13

Transformed into a National Application: No

Registration Date: 1989-11-28

Register: Principal

Law Office Assigned: (NOT AVAILABLE)

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Current Location: 900 -File Repository (Franconia)

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LAST APPLICANT(S)/OWNER(S) OF RECORD

1. NOVARTIS AG

Address:
NOVARTIS AG
CH-4002
BASEL
Switzerland
Legal Entity Type: Corporation
State or Country of Incorporation: Switzerland

GOODS AND/OR SERVICES

International Class: 005
Class Status: Active

PHARMACEUTICAL PREPARATION, NAMELY, ANTIFUNGAL FOR TOPICAL, SYSTEMIC AND VAGINAL USE
Basis: 1(a)
First Use Date: 1987-12-23
First Use in Commerce Date: 1987-12-23

ADDITIONAL INFORMATION

(NOT AVAILABLE)

MADRID PROTOCOL INFORMATION

(NOT AVAILABLE)

PROSECUTION HISTORY

2004-12-04 - TEAS Change Of Correspondence Received

2004-11-18 - PAPER RECEIVED

2000-06-30 - First renewal 10 year

2000-06-30 - Section 8 (10-year) accepted/ Section 9 granted

1999-11-17 - Combined Section 8 (10-year)/Section 9 filed

1996-06-17 - Section 8 (6-year) accepted & Section 15 acknowledged

1995-11-06 - Section 8 (6-year) and Section 15 Filed

1989-11-28 - Registered - Principal Register

1989-09-05 - Published for opposition

1989-08-05 - Notice of publication

1989-05-20 - Approved for Pub - Principal Register (Initial exam)

1989-05-09 - Assigned To Examiner

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Domestic Representative
NOVARTIS CORPORATION

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Physician's Desk Reference for Non-Prescription Drugs

Lamisil AT Cream(Novartis Consumer)

BODY:

Active Ingredient: Purpose:

Terbinafine
hydrochloride 1% ..... Antifungal

Uses:

cures most athlete's foot (tinea pedis)cures most jock itch (tinea cruris) and ringworm (tinea corporis)relieves itching, burning, cracking and scaling which accompany these conditions

Warnings:

For external use only

Do not use on nails or scalp

in or near the mouth or the eyesfor vaginal yeast infections

When using this product do not get into the eyes. If eye contact occurs, rinse thoroughly with water.

Stop use and ask a doctor if too much irritation occurs or gets worse.

Keep out of reach of children. If swallowed, get medical help or contact a poison control center right away.

Directions:

adults and children 12 years and over
use the tip of the cap to break the seal and open the tubewash the affected skin with soap and water and dry completely before applyingfor athlete's foot wear well-fitting, ventilated shoes. Change shoes and socks at least once daily. between the toes only: apply twice a day (morning and night) for 1 week or as directed by a doctor. See Image on the bottom or sides of the foot: apply twice a day (morning and night) for 2 weeks or as directed by a doctor. See Image for jock itch and ringworm: apply once a day (morning or night) for 1 week or as directed by a doctor.wash hands after each usechildren under 12 years: ask a doctor

Other Information: do not use if seal on tube is broken or is not visible

store at controlled room temperature 20-25 deg. C (68-77 deg. F)

Inactive Ingredients: benzyl alcohol, cetyl alcohol, cetyl palmitate, isopropyl myristate, polysorbate 60, purified water, sodium hydroxide, sorbitan monostearate, stearyl alcohol.

How Supplied: Athlete's Foot — Net wt. 12g (.42 oz.) tube and 24g (.85 oz.) tube, Jock Itch — Net wt. 12g (.42 oz.) tube.

Questions? call 1-800-452-0051 24 hours a day, 7 days a week.

Novartis Consumer Health, Inc.

Parsippany, NJ 07054-0622 ©2002

PRODUCT PHOTO(S): NOTE: These photos can be used only for identification by shape, color, and imprint. They do not depict actual *or relative* size.

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See Image

LANGUAGE: ENGLISH

LOAD-DATE: February 11, 2005

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This page was generated by the TARR system on 2006-06-28 20:34:28 ET

Serial Number: 71605494 Assignment Information

Registration Number: 549313

Mark (words only): MAALOX

Standard Character claim: No

Current Status: This registration has been renewed.

Date of Status: 2001-12-14

Filing Date: 1950-10-27

Transformed into a National Application: No

Registration Date: 1951-10-09

Register: Principal

Law Office Assigned: (NOT AVAILABLE)

If you are the applicant or applicant's attorney and have questions about this file, please contact the Trademark Assistance Center at TrademarkAssistanceCenter@uspto.gov

Current Location: 900 -File Repository (Franconia)

Date In Location: 2001-12-17

LAST APPLICANT(S)/OWNER(S) OF RECORD

1. AVENTIS PHARMACEUTICALS PRODUCTS INC.

Address:
AVENTIS PHARMACEUTICALS PRODUCTS INC.
ROUTE #202-206 N/ P. O./ BOX 6800 (MAIL STOP: EMC-G1-914
BRIDGEWATER, NJ 088070800
United States
Legal Entity Type: Corporation
State or Country of Incorporation: Delaware

GOODS AND/OR SERVICES

U.S. Class: 018 (International Class 005)
Class Status: Active

ANTACID
Basis: 1(a)
First Use Date: 1949-08-04
First Use in Commerce Date: 1949-08-12

ADDITIONAL INFORMATION

(NOT AVAILABLE)

MADRID PROTOCOL INFORMATION

(NOT AVAILABLE)

PROSECUTION HISTORY

2001-12-14 - Third renewal 10 year

2001-12-14 - Section 8 (10-year) accepted/ Section 9 granted

2001-10-01 - Combined Section 8 (10-year)/Section 9 filed

1991-07-17 - Second renewal 10 year

1991-06-13 - Section 9 filed/check record for Section 8

1971-10-09 - First renewal

CORRESPONDENCE INFORMATION

Correspondent
SUSAN CHWAT-MYERS
AVENTIS PHARMACEUTICALS PRODUCTS INC
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ROUTE #202-206/ P O BOX 6800
BRIDGEWATER NJ 088070800

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Physician's Desk Reference for Non-Prescription Drugs

Maalox Regular Strength Antacid/Antigas Liquid(Novartis Consumer)

BODY:

Liquids

Cooling MintSmooth Cherry

DESCRIPTION

Maalox(R) Antacid/Anti-Gas, a balanced combination of magnesium and aluminum hydroxides plus simethicone, is an Antacid/Anti-Gas product to provide relief of acid indigestion, heartburn, sour stomach, upset stomach associated with these symptoms, and relief of pressure and bloating commonly referred to as gas.

Active Ingredients	Maalox Suspension 5 mL teaspoon	Purpose
Aluminum Hydroxide (equivalent to dried gel, USP)	200 mg	Antacid
Magnesium Hydroxide	200 mg	Antacid
Simethicone	20 mg	Antigas

Uses: For the relief of

acid indigestionheartburnsour stomachupset stomach associated with these symptomsbloating and pressure commonly referred to as gas

Inactive Ingredients: butylparaben, carboxymethylcellulose sodium, flavor, hypromellose, microcrystalline cellulose, propylparaben, purified water, saccharin sodium, sorbitol.

Maalox(R) Suspension
Per 2 Tsp. (10 mL)
(Minimum Recommended Dosage)

Acid neutralizing capacity	19.4 mEq

WARNINGS

Ask a doctor before use if you have kidney disease

Ask a doctor or pharmacist before use if you are taking a prescription drug. Antacids may interact with certain prescription drugs.

Stop use and ask a doctor if symptoms last for more than 2 weeks

Keep out of reach of children.

DIRECTIONS

shake well before usingAdults/children 12 years and older: take 2 to 4 teaspoonsful four times a day or as directed by a physiciando not take more than 16 teaspoonsful in 24 hours or use the maximum dosage for more than 2 weeks.Children under 12 years: consult a physician

PROFESSIONAL LABELING
INDICATIONS

As an antacid for symptomatic relief of hyperacidity associated with the diagnosis of peptic ulcer, gastritis, peptic esophagitis, gastric hyperacidity, or hiatal hernia. As an antiflatulent to alleviate the symptoms of gas, including postoperative gas pain.

WARNINGS

Prolonged use of aluminum-containing antacids in patients with renal failure may result in or worsen dialysis osteomalacia. Elevated tissue aluminum levels contribute to the development of the dialysis encephalopathy and osteomalacia syndromes. Small amounts of aluminum are absorbed from the gastrointestinal tract and renal excretion of aluminum is impaired in renal failure. Aluminum is not well removed by dialysis because it is bound to albumin and transferrin, which do not cross dialysis membranes. As a result, aluminum is deposited in bone, and dialysis osteomalacia may develop when large amounts of aluminum are ingested orally by patients with impaired renal function.

Aluminum forms insoluble complexes with phosphate in the gastrointestinal tract, thus decreasing phosphate absorption. Prolonged use of aluminum-containing antacids by normophosphatemic patients may result in hypophosphatemia if phosphate intake is not adequate. In its more severe forms, hypophosphatemia can lead to anorexia, malaise, muscle weakness, and osteomalacia.

Advantages: In addition to the fast acting antacid ingredients, Aluminum Hydroxide and Magnesium Hydroxide, MAALOX(R) Regular Strength Antacid/Antigas contains the powerful antigas ingredient, simethicone, to provide concurrent fast relief from discomfort associated with gas.

HOW SUPPLIED

Maalox(R) Regular Strength Cooling Mint Suspension is available in plastic bottles of 5 oz. (148 mL), 12 oz. (355 mL) and 26 oz. (769 mL)

Maalox(R) Regular Strength Smooth Cherry Suspension is available in plastic bottles of 12 oz. (355 mL)

PRODUCT PHOTO(S): NOTE: These photos can be used only for identification by shape, color, and imprint. They do not depict actual *or relative* size.

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LANGUAGE: ENGLISH

LOAD-DATE: February 11, 2005

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Serial Number: 73637147 Assignment Information

Registration Number: 1452879

Mark (words only): THERAFLU

Standard Character claim: No

Current Status: Section 8 and 15 affidavits have been accepted and acknowledged.

Date of Status: 1993-12-17

Filing Date: 1986-12-24

Transformed into a National Application: No

Registration Date: 1987-08-18

Register: Principal

Law Office Assigned: (NOT AVAILABLE)

If you are the applicant or applicant's attorney and have questions about this file, please contact the Trademark Assistance Center at TrademarkAssistanceCenter@uspto.gov

Current Location: 900 -File Repository (Franconia)

Date In Location: 1994-01-31

LAST APPLICANT(S)/OWNER(S) OF RECORD

1. SANDOZ AG (SANDOZ LTD. SANDOZ S.A.)

Address:
SANDOZ AG (SANDOZ LTD. SANDOZ S.A.)
LICHSTRASSE 35
BASLE
Switzerland
Legal Entity Type: Corporation
State or Country of Incorporation: Switzerland

GOODS AND/OR SERVICES

International Class: 005
Class Status: Active

COUGH AND COLD PREPARATION
Basis: 1(a)
First Use Date: 1986-10-30
First Use in Commerce Date: 1986-10-30

ADDITIONAL INFORMATION

(NOT AVAILABLE)

MADRID PROTOCOL INFORMATION

(NOT AVAILABLE)

PROSECUTION HISTORY

1993-12-17 - Section 8 (6-year) accepted & Section 15 acknowledged

1993-08-02 - Section 8 (6-year) and Section 15 Filed

1992-08-17 - Section 8 (6-year) and Section 15 Filed

1987-08-18 - Registered - Principal Register

1987-05-26 - Published for opposition

1987-04-25 - Notice of publication

1987-03-16 - Approved for Pub - Principal Register (Initial exam)

1987-03-04 - Assigned To Examiner

CORRESPONDENCE INFORMATION

Correspondent
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BARRY A. SOLOMON
SANDOZ CORPORATION
59 ROUTE 10
EAST HANOVER, NJ 07936

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Physician's Desk Reference for Non-Prescription Drugs

TheraFlu Severe Cold Caplets(Novartis Consumer)

BODY:

Drug Facts

Active Ingredients:
(in each caplet) Purpose:

Acetaminophen
500 mg..... Pain reliever/Fever reducer

Chlorpheniramine maleate
2 mg..... Antihistamine

Dextromethorphan HBr
15 mg..... Cough suppressant

Pseudoephedrine HCl
30 mg..... Nasal decongestant

Uses: temporarily relieves these symptoms:

headache minor aches and pains runny nose sneezing itchy nose or throat itchy, watery eyes fever minor sore throat pain nasal and sinus congestion cough due to minor throat and bronchial irritation

Warnings:

Alcohol Warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take acetaminophen or any other pain relievers/fever reducers. Acetaminophen may cause liver damage.

Do not use if you are now taking a prescription monamine oxidase inhibitor (MAOI) (certain drugs for depression), psychiatric, or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.

with any other product containing acetaminophen (see Overdose Warning)

Ask a doctor before use if you have heart disease high blood pressure thyroid disease diabetes glaucoma a breathing problem such as emphysema, asthma, or chronic bronchitis

trouble urinating due to an enlarged prostate gland

cough that occurs with smoking, too much phlegm (mucus) or chronic cough that lasts

Ask a doctor or pharmacist before use if you are taking sedatives or tranquilizers.

When using this product do not use more than directed avoid alcoholic drinks

marked drowsiness may occuralcohol, sedatives, and tranquilizers may increase drowsinessbe careful when driving a motor vehicle or operating machineryexcitability may occur, especially in children

Stop use and ask a doctor if nervousness, dizziness, or sleeplessness occurs

symptoms do not improve for 7 days or occur with a fevercough persists for more than 7 days, comes back, or occurs with a fever, rash, or persistent headachesymptoms do not improve for 10 days (pain) or for 3 days (fever)sore throat persists for more than 2 days, and occurs with a fever, headache, rash, nausea, or vomiting. These could be signs of a serious condition.

If pregnant or breast-feeding, ask a health care professional before use.

Keep out of reach of children.

Overdose Warning: Taking more than the recommended dose can cause serious health problems, including serious liver damage. In case of overdose, get medical help or contact a poison control center right away. Prompt medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms.

Directions:

do not use more than directed (see Overdose Warning)take every 6 hours; not more than 8 caplets in 24 hoursadults and children 12 years of age and over: 2 caplets every 6 hourschildren under 12 years of age: consult a doctor

Other Information: each caplet contains: sodium 6 mg store at controlled room temperature 20-25 deg. C (68-77 deg. F)

Inactive Ingredients: colloidal silicon dioxide, croscarmellose sodium, D&C Yellow 10 aluminum lake, FD&C Blue 1 aluminum lake, FD&C Yellow 6 aluminum lake, gelatin, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, methylparaben, polydextrose, polyethylene glycol, pregelatinized starch, titanium dioxide, triacetin

How Supplied: 24 coated caplets

Novartis Consumer Health, Inc.

Parsippany, NJ 07054-0622

PRODUCT PHOTO(S): NOTE: These photos can be used only for identification by shape, color, and imprint. They do not depict actual *or relative* size.

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LANGUAGE: ENGLISH

LOAD-DATE: February 11, 2005

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This page was generated by the TARR system on 2006-06-28 20:36:53 ET

Serial Number: 78239975 Assignment Information

Registration Number: 2791532

Mark (words only): TRIAMINIC

Standard Character claim: No

Current Status: Registered.

Date of Status: 2003-12-09

Filing Date: 2003-04-21

Transformed into a National Application: No

Registration Date: 2003-12-09

Register: Principal

Law Office Assigned: LAW OFFICE 113

If you are the applicant or applicant's attorney and have questions about this file, please contact the Trademark Assistance Center at TrademarkAssistanceCenter@uspto.gov

Current Location: 900 -File Repository (Franconia)

Date In Location: 2003-12-15

LAST APPLICANT(S)/OWNER(S) OF RECORD

1. Novartis AG

Address:
Novartis AG
Lichtstrasse 35
Basel CH 4056
Switzerland
Legal Entity Type: Corporation
State or Country of Incorporation: Switzerland
Phone Number: 862-778-8038
Fax Number: 973-781-8060

GOODS AND/OR SERVICES

International Class: 005
Class Status: Active
cough, cold and allergy preparations
Basis: 1(a)
First Use Date: 1953-03-18
First Use in Commerce Date: 1953-03-18

ADDITIONAL INFORMATION

Prior Registration Number(s):
589662
1216342
1216345
1244111

MADRID PROTOCOL INFORMATION

(NOT AVAILABLE)

PROSECUTION HISTORY

2003-12-09 - Registered - Principal Register

2003-09-16 - Published for opposition

2003-08-27 - Notice of publication

2003-07-11 - Approved for Pub - Principal Register (Initial exam)

2003-07-11 - Previous allowance count withdrawn

2003-07-09 - Email Received

2003-07-08 - Approved for Pub - Principal Register (Initial exam)

2003-07-08 - Examiners amendment e-mailed

2003-06-30 - Assigned To Examiner

CORRESPONDENCE INFORMATION

Correspondent
Mary F. Leheny (Attorney of record)

Mary F. Leheny
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1 HEALTH PLZ BLDG 430
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Phone Number: 862-778-8038
Fax Number: 973-781-8060

Domestic Representative
Mary F. Leheny
Phone Number: 862-778-8038
Fax Number: 973-781-8060

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Physician's Desk Reference for Non-Prescription Drugs

Triaminic Chest & Nasal Congestion Liquid(Novartis Consumer)

BODY:

Drug Facts

Active Ingredients:

(in each 5 mL, 1 teaspoon): Purpose:

Guaifenesin,
USP, 50 mg ..... Expectorant

Pseudoephedrine HCl,
USP, 15 mg ..... Nasal decongestant

Uses: temporarily relieves these symptoms:

chest congestion by loosening phlegm (mucus) to help clear bronchial passageways nasal and sinus congestion

Warnings:

Do not use in a child who is taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if the child's prescription drug contains an MAOI, ask a doctor or pharmacist before giving this product.

Ask a doctor before use if the child has

heart disease high blood pressure

thyroid disease diabetes glaucoma

cough that occurs with too much phlegm (mucus) chronic cough that lasts or a breathing problem such as asthma or chronic bronchitis

When using this product

do not use more than directed

Stop use and ask a doctor if

nervousness, dizziness, or sleeplessness occur symptoms do not improve within 7 days or occur with a fever cough persists for more than 7 days, comes back, or occurs with a fever, rash, or persistent headache. These could be signs of a serious condition.

Keep out of reach of children. In case of overdose, get medical help or contact a poison control center right away.

Directions:

take every 4 to 6 hours; not more than 4 doses in 24 hours or as directed by a doctor

children 6 to under 12 years of age	2 teaspoons
children 2 to under 6 years of age	1 teaspoon
children under 2 years of age	ask a doctor

Other Information:

each teaspoon contains: sodium 2 mgcontains no aspirinstore at controlled room temperature 20-25 deg. C (68-77 deg. F)

Inactive Ingredients: benzoic acid, D&C Yellow 10, edetate disodium, FD&C Yellow 6, flavors, glycerin, polyethylene glycol, propylene glycol, purified water, sorbitol, sucrose

Questions? Call toll-free 1-800-452-0051 24 hours a day, 7 days a week.

For more information plus helpful tips visit www.triaminic.com

Novartis Consumer Health, Inc.

Parsippany, NJ 07054-0622 ©2004

How Supplied: 4 fl oz (118 mL)

PRODUCT PHOTO(S): NOTE: These photos can be used only for identification by shape, color, and imprint. They do not depict actual *or relative* size.

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LANGUAGE: ENGLISH

LOAD-DATE: February 11, 2005

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This page was generated by the TARR system on 2006-06-28 20:37:48 ET

Serial Number: 73792077 Assignment Information

Registration Number: 1569211

Mark (words only): CATAFLAM

Standard Character claim: No

Current Status: This registration has been renewed.

Date of Status: 2000-08-21

Filing Date: 1989-04-10

Transformed into a National Application: No

Registration Date: 1989-12-05

Register: Principal

Law Office Assigned: (NOT AVAILABLE)

If you are the applicant or applicant's attorney and have questions about this file, please contact the Trademark Assistance Center at TrademarkAssistanceCenter@uspto.gov

Current Location: 900 -File Repository (Franconia)

Date In Location: 2000-09-05

LAST APPLICANT(S)/OWNER(S) OF RECORD

1. NOVARTIS CORPORATION

Address:
NOVARTIS CORPORATION
608 FIFTH AVENUE
NEW YORK, NY 10020
United States
Legal Entity Type: Corporation
State or Country of Incorporation: New York

GOODS AND/OR SERVICES

International Class: 005
Class Status: Active

ANALGESICS
Basis: 1(a)
First Use Date: 1989-02-13
First Use in Commerce Date: 1989-02-13

ADDITIONAL INFORMATION

(NOT AVAILABLE)

MADRID PROTOCOL INFORMATION

(NOT AVAILABLE)

PROSECUTION HISTORY

2004-12-04 - TEAS Change Of Correspondence Received

2004-11-18 - PAPER RECEIVED

2000-08-21 - First renewal 10 year

2000-08-21 - Section 8 (10-year) accepted/ Section 9 granted

2000-01-07 - Combined Section 8 (10-year)/Section 9 filed

1996-10-28 - Section 15 acknowledged

1996-09-09 - Section 15 affidavit received

1996-06-06 - Section 8 (6-year) accepted

1995-11-22 - Section 8 (6-year) filed

1989-12-05 - Registered - Principal Register

1989-09-12 - Published for opposition

1989-09-12 - Published for opposition

1989-08-12 - Notice of publication

1989-06-14 - Approved for Pub - Principal Register (Initial exam)

CORRESPONDENCE INFORMATION

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Maury M. Tepper, III
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Raleigh NC 27602

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Physician's Desk Reference for Prescription Drugs

Cataflam Tablets(Novartis)

BODY:

The following prescribing information is based on official labeling in effect July 2005.

DESCRIPTION

Cataflam(R) (diclofenac potassium immediate-release tablets), is a benzeneacetic acid derivative. Cataflam is available as immediate-release tablets of 50 mg (light brown) for oral administration. The chemical name is 2-(2,6-dichlorophenyl)amino benzeneacetic acid, monopotassium salt. The molecular weight is 334.25. Its molecular formula is C[14] H[10] Cl[2] NKO[2] , and it has the following structural formula

See Image

The inactive ingredients in Cataflam include: calcium phosphate, colloidal silicon dioxide, iron oxides, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, sodium starch glycolate, maize starch, sucrose, talc, titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Cataflam(R) (diclofenac potassium immediate-release tablets) is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of Cataflam, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

Pharmacokinetics

Absorption

Diclofenac is 100% absorbed after oral administration compared to IV administration as measured by urine recovery. However, due to first-pass metabolism, only about 50% of the absorbed dose is systemically available (see Table 1). In some fasting volunteers, measurable plasma levels are observed within 10 minutes of dosing with Cataflam. Peak plasma levels are achieved approximately 1 hour in fasting normal volunteers, with a range of .33 to 2 hours. Food has no significant effect on the extent of diclofenac absorption. However, there is usually a delay in the onset of absorption and a reduction in peak plasma levels of approximately 30%.

Table 1. Pharmacokinetic Parameters for Diclofenac

PK Parameter	Normal Healthy Adults (20-52 yrs.)	
	Mean	Coefficient of Variation (%)
Absolute Bioavailability	55	40

Table 1. Pharmacokinetic Parameters for Diclofenac

(%) N = 7		
T[max] (hr) N = 65	1.0	76
Oral Clearance (CL/F; mL/min) N = 61	622	21
Renal Clearance (% unchanged drug in urine) N = 7	<1	—
Apparent Volume of Distribution (V/F; L/kg) N = 61	1.3	33
Terminal Half-life (hr) N = 48	1.9	29

Distribution

The apparent volume of distribution (V/F) of diclofenac potassium is 1.3 L/kg.

Diclofenac is more than 99% bound to human serum proteins, primarily to albumin. Serum protein binding is constant over the concentration range (0.15–105 micro g/mL) achieved with recommended doses.

Diclofenac diffuses into and out of the synovial fluid. Diffusion into the joint occurs when plasma levels are higher than those in the synovial fluid, after which the process reverses and synovial fluid levels are higher than plasma levels. It is not known whether diffusion into the joint plays a role in the effectiveness of diclofenac.

Metabolism

Five diclofenac metabolites have been identified in human plasma and urine. The metabolites include 4'-hydroxy-, 5-hydroxy-, 3'-hydroxy-, 4',5-dihydroxy-and 3'-hydroxy-4'-methoxy diclofenac. In patients with renal dysfunction, peak concentrations of metabolites 4'-hydroxy-and 5-hydroxy-diclofenac were approximately 50% and 4% of the parent compound after single oral dosing compared to 27% and 1% in normal healthy subjects. However, diclofenac metabolites undergo further glucuronidation and sulfation followed by biliary excretion.

One diclofenac metabolite 4'-hydroxy-diclofenac has very weak pharmacologic activity.

Excretion

Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Little or no free unchanged diclofenac is excreted in the urine. Approximately 65% of the dose is excreted in the urine and approximately 35% in the bile as conjugates of unchanged diclofenac plus metabolites. Because renal elimination is not a significant pathway of elimination for unchanged diclofenac, dosing adjustment in patients with mild to moderate renal dysfunction is not necessary. The terminal half-life of unchanged diclofenac is approximately 2 hours.

Special Populations

Pediatric: The pharmacokinetics of Cataflam has not been investigated in pediatric patients.

Race: Pharmacokinetics differences due to race have not been identified.

Hepatic Insufficiency: Hepatic metabolism accounts for almost 100% of Cataflam elimination, so patients with hepatic

disease may require reduced doses of Cataflam compared to patients with normal hepatic function.

Renal Insufficiency: Diclofenac pharmacokinetics has been investigated in subjects with renal insufficiency. No differences in the pharmacokinetics of diclofenac have been detected in studies of patients with renal impairment. In patients with renal impairment (inulin clearance 60-90, 30-60, and <30 mL/min; N=6 in each group), AUC values and elimination rate were comparable to those in healthy subjects.

INDICATIONS AND USAGE

Cataflam(R) (diclofenac potassium immediate-release tablets) is indicated:

For treatment of primary dysmenorrheaFor relief of mild to moderate painFor relief of signs and symptoms of osteoarthritisFor relief of signs and symptoms of rheumatoid arthritis

CONTRAINDICATIONS

Cataflam(R) (diclofenac potassium immediate-release tablets) is contraindicated in patients with known hypersensitivity to diclofenac. Cataflam should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see WARNINGS - Anaphylactoid Reactions and PRECAUTIONS - Preexisting Asthma).

WARNINGS

Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation:

Serious gastrointestinal toxicity such as inflammation, bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2%-4% of patients treated for one year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Studies have shown that patients with *a prior history of peptic ulcer disease and/or gastrointestinal bleeding* and who use NSAIDs, have a greater than 10-fold risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.

Anaphylactoid Reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to Cataflam(R)

(diclofenac potassium immediate-release tablets). Cataflam should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs. (See CONTRAINDICATIONS and PRECAUTIONS - Preexisting Asthma .) Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Advanced Renal Disease

In cases with advanced kidney disease, treatment with Cataflam is not recommended. If NSAID therapy, however, must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS - Renal Effects).

Pregnancy

In late pregnancy, as with other NSAIDs, Cataflam should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS

General

Cataflam(R) (diclofenac potassium immediate-release tablets) cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of Cataflam in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

Hepatic Effects

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including Cataflam. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continued therapy. Based on this experience, in patients on chronic treatment with Cataflam, periodic monitoring of transaminases is recommended (see PRECAUTIONS - Laboratory Tests). Notable elevations of ALT or AST (three or more times the upper limit of normal) have been reported in approximately 2%-4% of patients, including marked elevations (eight or more times the upper limit of normal) in about 1% of patients in clinical trials with diclofenac. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes have been reported.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with Cataflam. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), Cataflam should be discontinued.

Renal Effects

Caution should be used when initiating treatment with Cataflam in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with Cataflam. Caution is also recommended in patients with preexisting kidney disease (see WARNINGS - Advanced Renal Disease).

As with other NSAIDs, long-term administration of diclofenac has resulted in renal papillary necrosis and other renal medullary changes. Renal toxicity has also been seen in patients in which renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which

may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is usually followed by recovery to the pretreatment state.

Cataflam metabolites are eliminated primarily by the kidneys. The extent to which the metabolites may accumulate in patients with renal failure has not been studied. As with other NSAIDs, metabolites of which are excreted by the kidney, patients with significantly impaired renal function should be more closely monitored.

Hematological Effects

Anemia is sometimes seen in patients receiving NSAIDs, including Cataflam. This may be due to fluid retention, GI loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including Cataflam, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

All drugs which inhibit the biosynthesis of prostaglandins may interfere to some extent with platelet function and vascular responses to bleeding.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Cataflam does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT). Patients receiving Cataflam who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Fluid Retention and Edema

Fluid retention and edema have been observed in some patients taking NSAIDs. Therefore, as with other NSAIDs, Cataflam should be used with caution in patients with fluid retention, hypertension, or heart failure.

Preexisting Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross-reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, Cataflam should not be administered to patients with this form of aspirin sensitivity and should be used with caution in all patients with preexisting asthma.

Information for Patients

Cataflam, like other drugs of its class, can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative sign or symptoms. Patients should be apprised of the importance of this follow-up (see WARNINGS - Risk of Gastrointestinal Ulceration, Bleeding and Perforation).

Patients should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, weight gain, or edema.

Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

Patients should also be instructed to seek immediate emergency help in the case of an anaphylactoid reaction (see WARNINGS).

In late pregnancy, as with other NSAIDs, Cataflam should be avoided because it will cause premature closure of the ductus arteriosus.

Laboratory Tests

Patients on long-term treatment with NSAIDs, should have their CBC and a chemistry profile (including transaminases) checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash, etc.) or if abnormal liver tests persist or worsen, Cataflam should be discontinued.

Drug Interactions

Aspirin: When Cataflam is administered with aspirin, its protein binding is reduced. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of diclofenac and aspirin is not generally recommended because of the potential of increased adverse effects.

Methotrexate: NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

Cyclosporine: Cataflam, like other NSAIDs, may affect renal prostaglandins and increase the toxicity of certain drugs. Therefore, concomitant therapy with Cataflam may increase cyclosporine's nephrotoxicity. Caution should be used when Cataflam is administered concomitantly with cyclosporine.

ACE-inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors.

Furosemide: Clinical studies, as well as post-marketing observations, have shown that Cataflam can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure (see PRECAUTIONS - Renal Effects), as well as to assure diuretic efficacy.

Lithium: NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Warfarin: The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

Pregnancy

Teratogenic Effects: Pregnancy Category C

Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women.

Nonteratogenic Effects: Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.

Labor and Delivery

In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. The effects of Cataflam on labor and delivery in pregnant women are unknown.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Cataflam, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

As with any NSAIDs, caution should be exercised in treating the elderly (65 years and older).

ADVERSE REACTIONS

In 718 patients treated for shorter periods, i.e., 2 weeks or less, with Cataflam(R) (diclofenac potassium immediate-release tablets), adverse reactions were reported one-half to one-tenth as frequently as by patients treated for longer periods. In a 6-month, double-blind trial comparing Cataflam (N=196) versus Voltaren(R) (diclofenac sodium delayed-release tablets) (N=197) versus ibuprofen (N=197), adverse reactions were similar in nature and frequency.

In patients taking Cataflam or other NSAIDs, the most frequently reported adverse experiences occurring in approximately 1%-10% of patients are:

Gastrointestinal experiences including: abdominal pain, constipation, diarrhea, dyspepsia, flatulence, gross bleeding/perforation, heartburn, nausea, GI ulcers (gastric/duodenal) and vomiting.

Abnormal renal function, anemia, dizziness, edema, elevated liver enzymes, headaches, increased bleeding time, pruritus, rashes and tinnitus.

Additional adverse experiences reported occasionally include:

Body as a Whole: fever, infection, sepsis

Cardiovascular System: congestive heart failure, hypertension, tachycardia, syncope

Digestive System: dry mouth, esophagitis, gastric/peptic ulcers, gastritis, gastrointestinal bleeding, glossitis, hematemesis, hepatitis, jaundice

Hemic and Lymphatic System: ecchymosis, eosinophilia, leukopenia, melena, purpura, rectal bleeding, stomatitis, thrombocytopenia

Metabolic and Nutritional: weight changes

Nervous System: anxiety, asthenia, confusion, depression, dream abnormalities, drowsiness, insomnia, malaise, nervousness, paresthesia, somnolence, tremors, vertigo

Respiratory System: asthma, dyspnea

Skin and Appendages: alopecia, photosensitivity, sweating increased

Special Senses: blurred vision

Urogenital System: cystitis, dysuria, hematuria, interstitial nephritis, oliguria/polyuria, proteinuria, renal failure

Other adverse reactions, which occur rarely are:

Body as a Whole: anaphylactic reactions, appetite changes, death

Cardiovascular System: arrhythmia, hypotension, myocardial infarction, palpitations, vasculitis

Digestive System: colitis, eructation, liver failure, pancreatitis

Hemic and Lymphatic System: agranulocytosis, hemolytic anemia, aplastic anemia, lymphadenopathy, pancytopenia

Metabolic and Nutritional: hyperglycemia

Nervous System: convulsions, coma, hallucinations, meningitis

Respiratory System: respiratory depression, pneumonia

Skin and Appendages: angioedema, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, urticaria

Special Senses: conjunctivitis, hearing impairment.

OVERDOSAGE

Symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose (5 to 10 times the usual dose). Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

DOSAGE AND ADMINISTRATION

As with other NSAIDs, the lowest dose should be sought for each patient. Therefore, after observing the response to initial therapy with Cataflam(R) (diclofenac potassium immediate-release tablets), the dose and frequency should be adjusted to suit an individual patient's needs.

For treatment of pain or primary dysmenorrhea the recommended dosage is 50 mg t.i.d. With experience, physicians may find that in some patients an initial dose of 100 mg of Cataflam, followed by 50-mg doses, will provide better relief.

For the relief of osteoarthritis the recommended dosage is 100-150 mg/day in divided doses, 50 mg b.i.d. or t.i.d.

For the relief of rheumatoid arthritis the recommended dosage is 150-200 mg/day in divided doses, 50 mg t.i.d. or q.i.d.

Different formulations of diclofenac Voltaren(R) (diclofenac sodium enteric-coated tablets); Voltaren(R)-XR (diclofenac sodium extended-release tablets); Cataflam(R) (diclofenac potassium immediate-release tablets) are not necessarily bioequivalent even if the milligram strength is the same.

HOW SUPPLIED

Cataflam Immediate-Release Tablets

50 mg - light brown, round, biconvex, sugar-coated tablets (imprinted Cataflam on one side and 50 on the other side in black ink)

Bottles of 100 ..... NDC 0078-0436-05

Do not store above 30 deg. C (86 deg. F).

Dispense in tight container (USP).

Manufactured by:

Patheon Inc., Whitby Operations

Ontario, Canada L1N 5Z5

Distributed by:

Novartis Pharmaceuticals Corp.

East Hanover, New Jersey 07936 REV: APRIL 2005 T2005-31 2357-25-05A

PRODUCT PHOTO(S): NOTE: These photos can be used only for identification by shape, color, and imprint. They do not depict actual *or relative* size.

The product samples shown here have been supplied by the manufacturer and reproduced in full color by PDR as a quick-reference identification aid. While every effort has been made to assure accurate reproduction, please remember that any visual identification should be considered preliminary. In cases of poisoning or suspected overdosage, the drug's identity should be verified by chemical analysis.
See Image

LANGUAGE: ENGLISH

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Serial Number: 73394129 Assignment Information

Registration Number: 1265560

Mark (words only): CLOZARIL

Standard Character claim: No

Current Status: This registration has been renewed.

Date of Status: 2004-03-04

Filing Date: 1982-09-29

Transformed into a National Application: No

Registration Date: 1984-01-31

Register: Principal

Law Office Assigned: (NOT AVAILABLE)

If you are the applicant or applicant's attorney and have questions about this file, please contact the Trademark Assistance Center at TrademarkAssistanceCenter@uspto.gov

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LAST APPLICANT(S)/OWNER(S) OF RECORD

1. NOVARTIS AG

Address:
NOVARTIS AG
BLDG. 430 ONE HEALTH PLAZA
EAST HANOVER, NJ 07936
United States
Legal Entity Type: Corporation
State or Country of Incorporation: Switzerland

GOODS AND/OR SERVICES

International Class: 005
Class Status: Active

a Neuroleptic Indicated for the Management of Manifestations of Acute and Chronic Psychotic Disorders
Basis: 1(a)
First Use Date: 1982-08-26
First Use in Commerce Date: 1982-08-26

ADDITIONAL INFORMATION

(NOT AVAILABLE)

MADRID PROTOCOL INFORMATION

(NOT AVAILABLE)

PROSECUTION HISTORY

2004-12-19 - TEAS Change Of Correspondence Received

2004-12-06 - PAPER RECEIVED

2004-03-04 - First renewal 10 year

2004-03-04 - Section 8 (10-year) accepted/ Section 9 granted

2004-01-14 - Combined Section 8 (10-year)/Section 9 filed

2004-01-14 - TEAS Section 8 & 9 Received

1990-05-30 - Section 8 (6-year) accepted & Section 15 acknowledged

1990-01-25 - Section 8 (6-year) and Section 15 Filed

1983-11-08 - Published for opposition

1984-01-31 - Registered - Principal Register

1983-11-08 - Published for opposition

1983-09-21 - Notice of publication

1983-08-22 - Approved for Pub - Principal Register (Initial exam)

1983-06-24 - Assigned To Examiner

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8 of 126 DOCUMENTS

Physician's Desk Reference for Prescription Drugs

Clozaril Tablets(Novartis)

BODY:

The following prescribing information is based on official labeling in effect July 2005.

Prescribing Information

Before prescribing CLOZARIL(R) (clozapine), the physician should be thoroughly familiar with the details of this prescribing information.

WARNING

AGRANULOCYTOSIS
BECAUSE OF A SIGNIFICANT RISK OF AGRANULOCYTOSIS, A POTENTIALLY LIFE-THREATENING ADVERSE EVENT, CLOZARIL(R) (CLOZAPINE) SHOULD BE RESERVED FOR USE IN (1) THE TREATMENT OF SEVERELY ILL PATIENTS WITH SCHIZOPHRENIA WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF STANDARD ANTIPSYCHOTIC DRUG TREATMENT, OR (2) FOR REDUCING THE RISK OF RECURRENT SUICIDAL BEHAVIOR IN PATIENTS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER WHO ARE JUDGED TO BE AT RISK OF RE-EXPERIENCING SUICIDAL BEHAVIOR.
PATIENTS BEING TREATED WITH CLOZAPINE MUST HAVE A BASELINE WHITE BLOOD CELL (WBC) COUNT AND ABSOLUTE NEUTROPHIL COUNT (ANC) BEFORE INITIATION OF TREATMENT AS WELL AS REGULAR WBC COUNTS AND ANCs DURING TREATMENT AND FOR AT LEAST 4 WEEKS AFTER DISCONTINUATION OF TREATMENT *(SEE* WARNINGS *)*.
CLOZAPINE IS AVAILABLE ONLY THROUGH A DISTRIBUTION SYSTEM THAT ENSURES MONITORING OF WBC COUNT AND ANC ACCORDING TO THE SCHEDULE DESCRIBED BELOW PRIOR TO DELIVERY OF THE NEXT SUPPLY OF MEDICATION *(SEE* WARNINGS *)*. SEIZURES
SEIZURES HAVE BEEN ASSOCIATED WITH THE USE OF CLOZAPINE. DOSE APPEARS TO BE AN IMPORTANT PREDICTOR OF SEIZURE, WITH A GREATER LIKELIHOOD AT HIGHER CLOZAPINE DOSES. CAUTION SHOULD BE USED WHEN ADMINISTERING CLOZAPINE TO PATIENTS HAVING A HISTORY OF SEIZURES OR OTHER PREDISPOSING FACTORS. PATIENTS SHOULD BE ADVISED NOT TO ENGAGE IN ANY ACTIVITY WHERE SUDDEN LOSS OF CONSCIOUSNESS COULD CAUSE SERIOUS RISK TO THEMSELVES OR OTHERS. *(SEE* WARNINGS *)*. MYOCARDITIS
ANALYSES OF POST-MARKETING SAFETY DATABASES SUGGEST THAT CLOZAPINE IS ASSOCIATED WITH AN INCREASED RISK OF FATAL MYOCARDITIS, ESPECIALLY DURING, BUT NOT LIMITED TO, THE FIRST MONTH OF THERAPY. IN PATIENTS IN WHOM MYOCARDITIS IS SUSPECTED, CLOZAPINE TREATMENT SHOULD BE PROMPTLY DISCONTINUED. *(SEE* WARNINGS *)*. OTHER ADVERSE CARDIOVASCULAR AND RESPIRATORY EFFECTS
ORTHOSTATIC HYPOTENSION, WITH OR WITHOUT SYNCOPE, CAN OCCUR WITH CLOZAPINE TREATMENT. RARELY, COLLAPSE CAN BE PROFOUND AND BE ACCOMPANIED BY RESPIRATORY AND/OR CARDIAC ARREST. ORTHOSTATIC HYPOTENSION IS MORE LIKELY TO OCCUR DURING INITIAL TITRATION IN ASSOCIATION WITH RAPID DOSE ESCALATION. IN PATIENTS WHO HAVE HAD EVEN A BRIEF INTERVAL OFF CLOZAPINE, i.e., 2 OR MORE DAYS SINCE THE LAST DOSE, TREATMENT SHOULD BE STARTED WITH 12.5 mg ONCE OR TWICE DAILY. *(SEE* WARNINGS *and* DOSAGE AND ADMINISTRATION *.)*
SINCE COLLAPSE, RESPIRATORY ARREST AND CARDIAC ARREST DURING INITIAL TREATMENT HAS OCCURRED IN PATIENTS WHO WERE BEING ADMINISTERED BENZODIAZEPINES OR OTHER PSYCHOTROPIC DRUGS, CAUTION IS ADVISED WHEN CLOZAPINE IS INITIATED IN PATIENTS TAKING A

BENZODIAZEPINE OR ANY OTHER PSYCHOTROPIC DRUG. *(SEE* WARNINGS .*)* INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS TREATED WITH ATYPICAL ANTIPSYCHOTIC DRUGS ARE AT AN INCREASED RISK OF DEATH COMPARED TO PLACEBO. ANALYSES OF SEVENTEEN PLACEBO-CONTROLLED TRIALS (MODAL DURATION OF 10 WEEKS) IN THESE PATIENTS REVEALED A RISK OF DEATH IN THE DRUG-TREATED PATIENTS OF BETWEEN 1.6 TO 1.7 TIMES THAT SEEN IN PLACEBO-TREATED PATIENTS. OVER THE COURSE OF A TYPICAL 10-WEEK CONTROLLED TRIAL, THE RATE OF DEATH IN DRUG-TREATED PATIENTS WAS ABOUT 4.5%, COMPARED TO A RATE OF ABOUT 2.6% IN THE PLACEBO GROUP. ALTHOUGH THE CAUSES OF DEATH WERE VARIED, MOST OF THE DEATHS APPEARED TO BE EITHER CARDIOVASCULAR (e.g., HEART FAILURE, SUDDEN DEATH) OR INFECTIOUS (e.g., PNEUMONIA) IN NATURE. CLOZARIL(R) (CLOZAPINE) IS NOT APPROVED FOR THE TREATMENT OF PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS.

DESCRIPTION

CLOZARIL(R) (clozapine), an atypical antipsychotic drug, is a tricyclic dibenzodiazepine derivative, 8-chloro-11-(4-methyl-1-piperazinyl)-5 *H*-dibenzo *b,e* 1,4 diazepine.

The structural formula is

See Image

CLOZARIL is available in pale yellow tablets of 25 mg and 100 mg for oral administration.

25 mg and 100 mg Tablets

Active Ingredient: clozapine is a yellow, crystalline powder, very slightly soluble in water.

Inactive Ingredients: colloidal silicon dioxide, lactose, magnesium stearate, povidone, starch (corn), and talc.

CLINICAL PHARMACOLOGY

Pharmacodynamics

CLOZARIL(R) (clozapine) is classified as an 'atypical' antipsychotic drug because its profile of binding to dopamine receptors and its effects on various dopamine-mediated behaviors differ from those exhibited by more typical antipsychotic drug products. In particular, although CLOZARIL does interfere with the binding of dopamine at D[1] , D[2] , D[3] and D[5] receptors, and has a high affinity for the D[4] receptor, it does not induce catalepsy nor inhibit apomorphine-induced stereotypy. This evidence, consistent with the view that CLOZARIL is preferentially more active at limbic than at striatal dopamine receptors, may explain the relative freedom of CLOZARIL from extrapyramidal side effects.

CLOZARIL also acts as an antagonist at adrenergic, cholinergic, histaminergic and serotonergic receptors.

Absorption, Distribution, Metabolism and Excretion

In man, CLOZARIL tablets (25 mg and 100 mg) are equally bioavailable relative to a clozapine solution. Following a dosage of 100 mg b.i.d., the average steady-state peak plasma concentration was 319 ng/mL (range: 102-771 ng/mL), occurring at the average of 2.5 hours (range: 1-6 hours) after dosing. The average minimum concentration at steady state was 122 ng/mL (range: 41-343 ng/mL), after 100 mg b.i.d. dosing. Food does not appear to affect the systemic bioavailability of CLOZARIL. Thus, CLOZARIL may be administered with or without food.

Clozapine is approximately 97% bound to serum proteins. The interaction between CLOZARIL and other highly protein-bound drugs has not been fully evaluated but may be important. *(See PRECAUTIONS .)*

Clozapine is almost completely metabolized prior to excretion and only trace amounts of unchanged drug are detected in the urine and feces. Approximately 50% of the administered dose is excreted in the urine and 30% in the feces. The demethylated, hydroxylated and N-oxide derivatives are components in both urine and feces. Pharmacological testing has shown the desmethyl metabolite to have only limited activity, while the hydroxylated and N-oxide derivatives were inactive.

The mean elimination half-life of clozapine after a single 75-mg dose was 8 hours (range: 4-12 hours), compared to a mean elimination half-life, after achieving steady state with 100 mg b.i.d. dosing, of 12 hours (range: 4-66 hours). A comparison of single-dose and multiple-dose administration of clozapine showed that the elimination half-life increased significantly after multiple dosing relative to that after single-dose administration, suggesting the possibility of concentration-dependent pharmacokinetics. However, at steady state, linearly dose-proportional changes with respect to AUC (area under the curve), peak and minimum clozapine plasma concentrations were observed after administration of 37.5 mg, 75 mg, and 150 mg b.i.d.

Human Pharmacology

In contrast to more typical antipsychotic drugs, CLOZARIL therapy produces little or no prolactin elevation.

As is true of more typical antipsychotic drugs, clinical EEG studies have shown that CLOZARIL increases delta and theta activity and slows dominant alpha frequencies. Enhanced synchronization occurs, and sharp wave activity and spike and wave complexes may also develop. Patients, on rare occasions, may report an intensification of dream activity during CLOZARIL therapy. REM sleep was found to be increased to 85% of the total sleep time. In these patients, the onset of REM sleep occurred almost immediately after falling asleep.

Clinical Trial Data (Reducing the Risk of Recurrent Suicidal Behavior in Patients with Schizophrenia or Schizoaffective Disorder Who are Judged to be at Risk of Re-experiencing Suicidal Behavior)

The effectiveness of CLOZARIL in reducing the risk of recurrent suicidal behavior was assessed in the International Suicide Prevention Trial (InterSePT(TM)), which was a prospective, randomized, international, parallel-group comparison of CLOZARIL vs. Zyprexa(R) [*] (olanzapine) in patients with schizophrenia or schizoaffective disorder (DSM-IV) who were judged to be at risk for re-experiencing suicidal behavior. Only about one-fourth of these patients (27%) were considered resistant to standard antipsychotic drug treatment, and the remainder were not. Patients met one of the following criteria:

They had attempted suicide within the 3 years prior to their baseline evaluation.They had been hospitalized to prevent a suicide attempt within the 3 years prior to their baseline evaluation.They demonstrated moderate-to-severe suicidal ideation with a depressive component within 1 week prior to their baseline evaluation.They demonstrated moderate-to-severe suicidal ideation accompanied by command hallucinations to do self-harm within 1 week prior to their baseline evaluation.

Dosing regimens for each treatment group were determined by individual investigators and were individualized by patient. Dosing was flexible, with a dose range of 200-900 mg/day for CLOZARIL and 5-20 mg/day for Zyprexa. For the 956 patients who received CLOZARIL or Zyprexa in this study, there was extensive use of concomitant psychotropics: 84% with antipsychotics; 65% with anxiolytics; 53% with antidepressants, and 28% with mood stabilizers. There was significantly greater use of concomitant psychotropic medications among the patients in the Zyprexa group.

The primary efficacy measure was time to (1) a significant suicide attempt, including a completed suicide, (2) hospitalization due to imminent suicide risk (including increased level of surveillance for suicidality for patients already hospitalized), or (3) worsening of suicidality severity as demonstrated by "much worsening" or "very much worsening" from baseline in the Clinical Global Impression of Severity of Suicidality as assessed by the Blinded Psychiatrist (CGI-SS-BP) scale. A determination of whether or not a reported event met criterion 1 or 2 above was made by the Suicide Monitoring Board (SMB, a group of experts blinded to patient data).

A total of 980 patients were randomized to the study and 956 received study medication. Sixty-two percent of the patients were diagnosed with schizophrenia, and the remainder (38%) were diagnosed with schizoaffective disorder. Only about one-fourth of the total patient population (27%) was identified as "treatment resistant" at baseline. There were more males than females in the study (61% of all patients were male). The mean age of patients entering the study was 37 years (range 18-69). Most patients were Caucasian (71%), 15% were Black, 1% were Oriental, and 13% were classified as being of "other" races.

Data from this study indicate that CLOZARIL had a statistically significant longer delay in the time to recurrent suicidal behavior in comparison with Zyprexa. This result should be interpreted only as evidence of the effectiveness of CLOZARIL in delaying time to recurrent suicidal behavior, and not a demonstration of the superior efficacy of CLOZARIL over Zyprexa.

The probability of experiencing (1) a significant suicide attempt, including a completed suicide, or (2) hospitalization due to imminent suicide risk (including increased level of surveillance for suicidality for patients already hospitalized) was lower for CLOZARIL patients than for Zyprexa patients at Week 104: CLOZARIL 24% vs. Zyprexa 32%; 95% C.I. of the difference: 2%, 14% (Figure 1).

See Image

INDICATIONS AND USAGE

Treatment-Resistant Schizophrenia

CLOZARIL(R) (clozapine) is indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia. Because of the significant risk of agranulocytosis and seizure associated with its use, CLOZARIL should be used only in patients who have failed to respond adequately to treatment with appropriate courses of standard drug treatments for schizophrenia, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs. *(See WARNINGS .)*

The effectiveness of CLOZARIL in a treatment-resistant schizophrenic population was demonstrated in a 6-week study comparing CLOZARIL and chlorpromazine. Patients meeting DSM-III criteria for schizophrenia and having a mean BPRS total score of 61 were demonstrated to be treatment resistant by history and by open, prospective treatment with haloperidol before entering into the double-blind phase of the study. The superiority of CLOZARIL to chlorpromazine was documented in statistical analyses employing both categorical and continuous measures of treatment effect.

Because of the significant risk of agranulocytosis and seizure, events which both present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be periodically re-evaluated.

Reduction in the Risk of Recurrent Suicidal Behavior in Schizophrenia or Schizoaffective Disorders

CLOZARIL is indicated for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk for re-experiencing suicidal behavior, based on history and recent clinical state. Suicidal behavior refers to actions by a patient that puts him/herself at risk for death.

The effectiveness of CLOZARIL in reducing the risk of recurrent suicidal behavior was demonstrated over a 2-year treatment period in the InterSePT Trial *(see Clinical Trial Data under CLINICAL PHARMACOLOGY)* . Therefore, CLOZARIL treatment to reduce the risk of suicidal behavior should be continued for at least 2 years *(see DOSAGE AND ADMINISTRATION)*.

The prescriber should be aware that a majority of patients in both treatment groups in InterSePT received other treatments as well to reduce suicide risk, such as antidepressants and other medications, hospitalization, and/or

psychotherapy. The contributions of these additional measures are unknown.

CONTRAINDICATIONS

CLOZARIL(R) (clozapine) is contraindicated in patients with a previous hypersensitivity to clozapine or any other component of this drug, in patients with myeloproliferative disorders, uncontrolled epilepsy, paralytic ileus, or a history of CLOZARIL-induced agranulocytosis or severe granulocytopenia. As with more typical antipsychotic drugs, CLOZARIL is contraindicated in severe central nervous system depression or comatose states from any cause.

CLOZARIL should not be used simultaneously with other agents having a well-known potential to cause agranulocytosis or otherwise suppress bone marrow function. The mechanism of CLOZARIL-induced agranulocytosis is unknown; nonetheless, it is possible that causative factors may interact synergistically to increase the risk and/or severity of bone marrow suppression.

WARNINGS

General

INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS TREATED WITH ATYPICAL ANTIPSYCHOTIC DRUGS ARE AT AN INCREASED RISK OF DEATH COMPARED TO PLACEBO. CLOZARIL(R) (clozapine) IS NOT APPROVED FOR THE TREATMENT OF PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS *(SEE* BOXED WARNING *)*.

AGRANULOCYTOSIS

BECAUSE OF THE SIGNIFICANT RISK OF AGRANULOCYTOSIS, A POTENTIALLY LIFE-THREATENING ADVERSE EVENT *(SEE FOLLOWING)*, CLOZARIL(R) (clozapine) SHOULD BE RESERVED FOR USE IN THE FOLLOWING INDICATIONS: 1) FOR TREATMENT OF SEVERELY ILL SCHIZOPHRENIC PATIENTS WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF STANDARD DRUG TREATMENT FOR SCHIZOPHRENIA, EITHER BECAUSE OF INSUFFICIENT EFFECTIVENESS OR THE INABILITY TO ACHIEVE AN EFFECTIVE DOSE DUE TO INTOLERABLE ADVERSE EFFECTS FROM THOSE DRUGS. CONSEQUENTLY, BEFORE INITIATING TREATMENT WITH CLOZARIL(R) (clozapine); IT IS STRONGLY RECOMMENDED THAT A PATIENT BE GIVEN AT LEAST 2 TRIALS, EACH WITH A DIFFERENT STANDARD DRUG PRODUCT FOR SCHIZOPHRENIA, AT AN ADEQUATE DOSE, AND FOR AN ADEQUATE DURATION. 2) FOR REDUCING THE RISK FOR RECURRENT SUICIDAL BEHAVIOR IN PATIENTS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER WHO ARE JUDGED TO BE AT RISK OF RE-EXPERIENCING SUICIDAL BEHAVIOR.

CLOZARIL(R) (clozapine) IS AVAILABLE ONLY THROUGH A DISTRIBUTION SYSTEM THAT ENSURES MONITORING OF WHITE BLOOD CELL (WBC) COUNT AND ABSOLUTE NEUTROPHIL COUNT (ANC) ACCORDING TO THE SCHEDULE DESCRIBED BELOW PRIOR TO DELIVERY OF THE NEXT SUPPLY OF MEDICATION.

AS DESCRIBED IN TABLE 1, PATIENTS WHO ARE BEING TREATED WITH CLOZARIL(R) (clozapine) MUST HAVE A BASELINE WBC COUNT AND ANC BEFORE INITIATION OF TREATMENT, AND A WBC COUNT AND ANC EVERY WEEK FOR THE FIRST 6 MONTHS. THEREAFTER, IF ACCEPTABLE WBC COUNTS AND ANC (WBC >/=3500/mm[3] and ANC >/=2000/mm[3]) HAVE BEEN MAINTAINED DURING THE FIRST 6 MONTHS OF CONTINUOUS THERAPY, WBC COUNTS AND ANC CAN BE MONITORED EVERY 2 WEEKS FOR THE NEXT 6 MONTHS. THEREAFTER, IF ACCEPTABLE WBC COUNTS AND ANC (WBC >/=3500/mm[3] and ANC >/=2000/mm[3]) HAVE BEEN MAINTAINED DURING THE SECOND 6 MONTHS OF CONTINUOUS THERAPY, WBC COUNT AND ANC CAN BE MONITORED EVERY 4 WEEKS.

WHEN TREATMENT WITH CLOZARIL(R) (clozapine) IS DISCONTINUED (REGARDLESS OF THE REASON), WBC COUNT AND ANC MUST BE MONITORED WEEKLY FOR AT LEAST 4 WEEKS FROM THE DAY OF DISCONTINUATION OR UNTIL WBC >/=3500/mm[3] AND ANC >/=2000/mm[3] .

Agranulocytosis

Background

Agranulocytosis, defined as an ANC of less than 500/mm[3] , has been estimated to occur in association with CLOZARIL(R) (clozapine) use at a cumulative incidence at 1 year of approximately 1.3%, based on the occurrence of 15 U.S. cases out of 1,743 patients exposed to CLOZARIL(R) (clozapine) during its clinical testing prior to domestic marketing. All of these cases occurred at a time when the need for close monitoring of WBC counts was already recognized. Agranulocytosis could prove fatal if not detected early and therapy interrupted. Of the 149 cases of agranulocytosis reported world wide in association with CLOZARIL(R) (clozapine) use as of December 31, 1989, 32% were fatal. However, few of these deaths occurred since 1977, at which time the knowledge of CLOZARIL(R) (clozapine)-induced agranulocytosis became more widespread, and close monitoring of WBC counts more widely practiced. In the U.S., under a weekly WBC count monitoring system with CLOZARIL(R) (clozapine), there have been 585 cases of agranulocytosis as of August 21, 1997; 19 were fatal (3%). During this period 150,409 patients received CLOZARIL(R) (clozapine). A hematologic risk analysis was conducted based upon the available information in the Clozaril(R) National Registry (CNR) for U.S. patients. Based upon a cut-off date of April 30, 1995, the incidence rates of agranulocytosis based upon a weekly monitoring schedule, rose steeply during the first two months of therapy, peaking in the third month. Among CLOZARIL(R) (clozapine) patients who continued the drug beyond the third month, the weekly incidence of agranulocytosis fell to a substantial degree. After 6 months, the weekly incidence of agranulocytosis declines still further, however, it never reaches zero. It should be noted that any type of reduction in the frequency of monitoring WBC counts may result in an increased incidence of agranulocytosis.

Risk Factors

Experience from clinical development, as well as from examples in the medical literature, suggest that patients who have developed agranulocytosis during CLOZARIL(R) (clozapine) therapy are at increased risk of subsequent episodes of agranulocytosis. Analysis of WBC count data from the Clozaril(R) National Registry also suggests that patients who have an initial episode of moderate leukopenia (3000/mm[3] >WBC >/=2000/mm[3]) are at an increased risk of subsequent episodes of agranulocytosis. Except for bone marrow suppression during initial CLOZARIL(R) (clozapine) therapy, there are no other established risk factors, based on worldwide experience, for the development of agranulocytosis in association with CLOZARIL(R) (clozapine) use. However, a disproportionate number of the U.S. cases of agranulocytosis occurred in patients of Jewish background compared to the overall proportion of such patients exposed during domestic development of CLOZARIL(R) (clozapine). Most of the U.S. cases of agranulocytosis occurred within 4-10 weeks of exposure but neither dose nor duration is a reliable predictor of this problem. Agranulocytosis associated with other antipsychotic drugs has been reported to occur with a greater frequency in women, the elderly and in patients who are cachectic or have serious underlying medical illness; such patients may also be at particular risk with CLOZARIL(R) (clozapine), although this has not been definitely demonstrated.

WBC Count and ANC Monitoring Schedule

Table 1 provides a summary of the frequency of monitoring that should occur based on various stages of therapy (e.g., initiation of therapy) or results from WBC count and ANC monitoring tests (e.g., moderate leukopenia). The text that follows should be consulted for additional details regarding the treatment of patients under the various conditions (e.g., severe leukopenia).

Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat or any other signs of infection occurring at any time during CLOZARIL(R) (clozapine) therapy. Such patients should have a WBC count and ANC performed promptly.

Table 1 Frequency of Monitoring Based on Stage of Therapy or Results from WBC Count and ANC Monitoring Tests

Situation	Hematological Values for Monitoring	Frequency of WBC and ANC * Monitoring
Initiation of Therapy	WBC >/=3500/mm[3] ANC >/=2000/mm[3] Note: Do not initiate in patients with 1) history of myeloproliferative disorder or 2) CLOZARIL(R) (clozapine)-induced agranulocytosis or granulocytopenia	Weekly for 6 months
6 Months - 12 Months of Therapy	All results for WBC >/=3500/mm[3] and ANC >/=2000/mm[3]	Every 2 weeks for 6 months
12 Months of Therapy	All results for WBC >/=3500/mm[3] and ANC >/=2000/mm[3]	Every 4 weeks ad infinitum
Immature Forms Present	N/A	Repeat WBC and ANC
Discontinuation of Therapy	N/A	Weekly for at least 4 weeks from day of discontinuation or until WBC >/=3500/mm[3] and ANC >2000/mm[3]
Substantial Drop in WBC	Single Drop or	
or ANC	Cumulative Drop within 3 Weeks of WBC >/=3000/mm[3] or ANC >/=1500/mm[3]	Repeat WBC and ANC If repeat values are 3000/mm[3] </=WBC </=3500/mm[3] and ANC <2000/mm[3] , then monitor twice weekly
Mild Leukopenia ---------- - Mild Granulocytopenia	3500/mm[3] >WBC >/=3000/mm[3] and/or 2000/mm[3] >ANC >/=1500/mm[3]	Twice weekly until WBC >3500/mm[3]] and ANC >2000/mm[3] then return to previous monitoring frequency
Moderate Leukopenia	3000/mm[3] >WBC	
---------- -- Moderate Granulocytopenia	>/=2000/mm[3]] and/or 1500/mm[3] >ANC >/=1000/mm[3]	Interrupt therapy Daily until WBC >3000/mm[3] and ANC >1500/mm[3]

Table 1 Frequency of Monitoring Based on Stage of Therapy or Results from WBC Count and ANC Monitoring Tests

		Twice weekly until WBC >3500/mm[3] and ANC >2000/mm[3] May rechallenge when WBC >3500/mm[3] and ANC >2000/mm[3] If rechallenged, monitor weekly for 1 year before returning to the usual monitoring schedule of every 2 weeks for 6 months and then every 4 weeks ad infinitum
Severe Leukopenia	WBC <2000/mm[3]	
---------- - Severe Granulocytopenia	and/or ANC <1000/mm[3]	Discontinue treatment and do not rechallenge patient Monitor until normal and for at least 4 weeks from day of discontinuation as follows: Daily until WBC >3000/mm[3] and ANC >1500/mm[3] Twice weekly until WBC >3500/mm[3] and ANC >2000/mm[3] Weekly after WBC >3500/mm[3]
Agranulocytosis	ANC </=500/mm[3]	Discontinue treatment and do not rechallenge patient Monitor until normal and for at least 4 weeks from day of discontinuation as follows: Daily until WBC >3000/mm[3] and ANC >1500/mm[3] Twice weekly until WBC >3500/mm[3] and ANC >2000/mm[3]

Table 1 Frequency of Monitoring Based on Stage of Therapy or Results from WBC Count and ANC Monitoring Tests

	Weekly after WBC >3500/mm[3]

*WBC=white blood cell count; ANC=absolute neutrophil count

Decrements in WBC Count and/or ANC

Consult Table 1 above to determine how to monitor patients who experience decrements in WBC count and ANC at any point during treatment. Additionally, patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection.

Non-rechallengeable Patients

If the total WBC count falls below 2000/mm[3] or the ANC falls below 1000/mm[3] , bone marrow aspiration should be considered to ascertain granulopoietic status and patients should not be rechallenged with CLOZARIL(R) (clozapine). Protective isolation with close observation may be indicated if granulopoiesis is determined to be deficient. Should evidence of infection develop, the patient should have appropriate cultures performed and an appropriate antibiotic regimen instituted.

Patients discontinued from CLOZARIL(R) (clozapine) therapy due to significant granulopoietic suppression have been found to develop agranulocytosis upon rechallenge, often with a shorter latency on re-exposure. To reduce the chances of rechallenge occurring in patients who have experienced significant bone marrow suppression during CLOZARIL(R) (clozapine) therapy, a single, national master file (i.e., Non-rechallengeable Database) is maintained confidentially.

Treatment of Rechallengeable Patients

Patients may be rechallenged with CLOZARIL(R) (clozapine) if their WBC count does not fall below 2000/mm[3] and the ANC does not fall below 1000/mm[3] . However, analysis of data from the Clozaril(R) National Registry suggests that patients who have an initial episode of moderate leukopenia (3000/mm[3] >WBC>/=2000/mm[3]) have up to a 12-fold increased risk of having a subsequent episode of agranulocytosis when rechallenged compared to the full cohort of patients treated with CLOZARIL(R) (clozapine). Although CLOZARIL(R) (clozapine) therapy may be resumed if no symptoms of infection develop, and when the WBC count rises above 3500/mm[3] and the ANC rises above 2000/mm[3] , prescribers are strongly advised to consider whether the benefit of continuing CLOZARIL(R) (clozapine) treatment outweighs the increased risk of agranulocytosis.

Analyses of the Clozaril(R) National Registry have shown an increased risk of having a subsequent episode of granulopoietic suppression up to a year after recovery from the initial episode. Therefore, as noted in Table 1 above, patients must undergo weekly WBC count and ANC monitoring for one year following recovery from an episode of moderate leukopenia and/or moderate granulocytopenia regardless of when the episode develops. If acceptable WBC counts and ANC (WBC >/=3500/mm[3] and ANC >/=2000/mm[3]) have been maintained during the year of weekly monitoring, WBC counts can be monitored every 2 weeks for the next 6 months. If acceptable WBC counts and ANC (WBC >/=3500/mm[3] and ANC >/=2000/mm[3]) continue to be maintained during the 6 months of every 2 week monitoring, WBC counts can be monitored every 4 weeks thereafter, ad infinitum.

Interruptions in Therapy

Figure 2 provides instructions regarding reinitiating therapy and subsequently the frequency of WBC count and ANC monitoring after a period of interruption.

See Image

Eosinophilia

In clinical trials, 1% of patients developed eosinophilia, which, in rare cases, can be substantial. If a differential count reveals a total eosinophil count above 4000/mm[3] , CLOZARIL therapy should be interrupted until the eosinophil count falls below 3000/mm[3] .

Seizures

Seizure has been estimated to occur in association with CLOZARIL use at a cumulative incidence at one year of approximately 5%, based on the occurrence of one or more seizures in 61 of 1,743 patients exposed to CLOZARIL during its clinical testing prior to domestic marketing (i.e., a crude rate of 3.5%). Dose appears to be an important predictor of seizure, with a greater likelihood of seizure at the higher CLOZARIL doses used.

Caution should be used in administering CLOZARIL to patients having a history of seizures or other predisposing factors. Because of the substantial risk of seizure associated with CLOZARIL use, patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others, e.g., the operation of complex machinery, driving an automobile, swimming, climbing, etc.

Myocarditis

Post-marketing surveillance data from four countries that employ hematological monitoring of clozapine-treated patients revealed: 30 reports of myocarditis with 17 fatalities in 205,493 U.S. patients (August 2001); 7 reports of myocarditis with 1 fatality in 15,600 Canadian patients (April 2001); 30 reports of myocarditis with 8 fatalities in 24,108 U.K. patients (August 2001); 15 reports of myocarditis with 5 fatalities in 8,000 Australian patients (March 1999). These reports represent an incidence of 5.0, 16.3, 43.2, and 96.6 cases/100,000 patient-years, respectively. The number of fatalities represent an incidence of 2.8, 2.3, 11.5, and 32.2 cases/100,000 patient-years, respectively.

The overall incidence rate of myocarditis in patients with schizophrenia treated with antipsychotic agents is unknown. However, for the established market economies (WHO), the incidence of myocarditis is 0.3 cases/100,000 patient-years and the fatality rate is 0.2 cases/100,000 patient-years. Therefore, the rate of myocarditis in clozapine-treated patients appears to be 17-322 times greater than the general population and is associated with an increased risk of fatal myocarditis that is 14-161 times greater than the general population.

The total reports of myocarditis for these four countries was 82 of which 51 (62%) occurred within the first month of clozapine treatment, 25 (31%) occurred after the first month of therapy and 6 (7%) were unknown. The median duration of treatment was 3 weeks. Of 5 patients rechallenged with clozapine, 3 had a recurrence of myocarditis. Of the 82 reports, 31 (38%) were fatal and 25 patients who died had evidence of myocarditis at autopsy. These data also suggest that the incidence of fatal myocarditis may be highest during the first month of therapy.

Therefore, the possibility of myocarditis should be considered in patients receiving CLOZARIL who present with unexplained fatigue, dyspnea, tachypnea, fever, chest pain, palpitations, other signs or symptoms of heart failure, or electrocardiographic findings such as ST-T wave abnormalities or arrhythmias. It is not known whether eosinophilia is a reliable predictor of myocarditis. Tachycardia, which has been associated with CLOZARIL treatment, has also been noted as a presenting sign in patients with myocarditis. Therefore, tachycardia during the first month of therapy warrants close monitoring for other signs of myocarditis.

Prompt discontinuation of CLOZARIL treatment is warranted upon suspicion of myocarditis. Patients with clozapine-related myocarditis should not be rechallenged with CLOZARIL.

Other Adverse Cardiovascular and Respiratory Effects

Orthostatic hypotension with or without syncope can occur with CLOZARIL treatment and may represent a continuing risk in some patients. Rarely (approximately 1 case per 3,000 patients), collapse can be profound and be accompanied by respiratory and/or cardiac arrest. Orthostatic hypotension is more likely to occur during initial titration in association with rapid dose escalation and may even occur on first dose. In one report, initial doses as low as 12.5 mg were associated with collapse and respiratory arrest. When restarting patients who have had even a brief interval off

CLOZARIL, i.e., 2 days or more since the last dose, it is recommended that treatment be reinitiated with one-half of a 25-mg tablet (12.5 mg) once or twice daily. *(See* DOSAGE AND ADMINISTRATION .*)*

Some of the cases of collapse/respiratory arrest/cardiac arrest during initial treatment occurred in patients who were being administered benzodiazepines; similar events have been reported in patients taking other psychotropic drugs or even CLOZARIL by itself. Although it has not been established that there is an interaction between CLOZARIL and benzodiazepines or other psychotropics, caution is advised when clozapine is initiated in patients taking a benzodiazepine or any other psychotropic drug.

Tachycardia, which may be sustained, has also been observed in approximately 25% of patients taking CLOZARIL, with patients having an average increase in pulse rate of 10-15 bpm. The sustained tachycardia is not simply a reflex response to hypotension, and is present in all positions monitored. Either tachycardia or hypotension may pose a serious risk for an individual with compromised cardiovascular function.

A minority of CLOZARIL-treated patients experience ECG repolarization changes similar to those seen with other antipsychotic drugs, including S-T segment depression and flattening or inversion of T waves, which all normalize after discontinuation of CLOZARIL. The clinical significance of these changes is unclear. However, in clinical trials with CLOZARIL, several patients experienced significant cardiac events, including ischemic changes, myocardial infarction, arrhythmias and sudden death. In addition, there have been post-marketing reports of congestive heart failure, pericarditis, and pericardial effusions. Causality assessment was difficult in many of these cases because of serious pre-existing cardiac disease and plausible alternative causes. Rare instances of sudden death have been reported in psychiatric patients, with or without associated antipsychotic drug treatment, and the relationship of these events to anti-psychotic drug use is unknown.

CLOZARIL should be used with caution in patients with known cardiovascular and/or pulmonary disease, and the recommendation for gradual titration of dose should be carefully observed.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including CLOZARIL. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

There have been several reported cases of NMS in patients receiving CLOZARIL alone or in combination with lithium or other CNS-active agents.

Tardive Dyskinesia

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of treatment, which patients are likely to develop the syndrome.

There are several reasons for predicting that CLOZARIL may be different from other antipsychotic drugs in its potential for inducing tardive dyskinesia, including the preclinical finding that it has a relatively weak dopamine-blocking effect and the clinical finding of a virtual absence of certain acute extrapyramidal symptoms, e.g., dystonia. A few cases of tardive dyskinesia have been reported in patients on CLOZARIL who had been previously treated with other antipsychotic agents, so that a causal relationship cannot be established. There have been no reports of tardive dyskinesia directly attributable to CLOZARIL alone. Nevertheless, it cannot be concluded, without more extended experience, that CLOZARIL is incapable of inducing this syndrome.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic drug treatment is withdrawn. Antipsychotic drug treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptom suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, CLOZARIL should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. As with any antipsychotic drug, chronic CLOZARIL use should be reserved for patients who appear to be obtaining substantial benefit from the drug. In such patients, the smallest dose and the shortest duration of treatment should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on CLOZARIL, drug discontinuation should be considered. However, some patients may require treatment with CLOZARIL despite the presence of the syndrome.

PRECAUTIONS

General

Because of the significant risk of agranulocytosis and seizure, both of which present a continuing risk over time, the

extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be periodically re-evaluated. Although it is not known whether the risk would be increased, it is prudent either to avoid CLOZARIL(R) (clozapine) or use it cautiously in patients with a previous history of agranulocytosis induced by other drugs.

Cardiomyopathy

Cases of cardiomyopathy have been reported in patients treated with clozapine. The reporting rate for cardiomyopathy in clozapine-treated patients in the U.S. (8.9 per 100,000 person-years) was similar to an estimate of the cardiomyopathy incidence in the U.S. general population derived from the 1999 National Hospital Discharge Survey data (9.7 per 100,000 person-years). Approximately 80% of clozapine-treated patients in whom cardiomyopathy was reported were less than 50 years of age; the duration of treatment with clozapine prior to cardiomyopathy diagnosis varied, but was >6 months in 65% of the reports. Dilated cardiomyopathy was most frequently reported, although a large percentage of reports did not specify the type of cardiomyopathy. Signs and symptoms suggestive of cardiomyopathy, particularly exertional dyspnea, fatigue, orthopnea, paroxysmal nocturnal dyspnea, and peripheral edema should alert the clinician to perform further investigations. If the diagnosis of cardiomyopathy is confirmed, the prescriber should discontinue clozapine unless the benefit to the patient clearly outweighs the risk.

Fever

During CLOZARIL therapy, patients may experience transient temperature elevations above 100.4 deg. F (38 deg. C), with the peak incidence within the first 3 weeks of treatment. While this fever is generally benign and self-limiting, it may necessitate discontinuing patients from treatment. On occasion, there may be an associated increase or decrease in WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infectious process or the development of agranulocytosis. In the presence of high fever, the possibility of Neuroleptic Malignant Syndrome (NMS) must be considered. There have been several reports of NMS in patients receiving CLOZARIL, usually in combination with lithium or other CNS-active drugs. *(See Neuroleptic Malignant Syndrome NMS, under WARNINGS .)*

Pulmonary Embolism

The possibility of pulmonary embolism should be considered in patients receiving CLOZARIL who present with deep vein thrombosis, acute dyspnea, chest pain or with other respiratory signs and symptoms. As of December 31, 1993 there were 18 cases of fatal pulmonary embolism in association with CLOZARIL therapy in users 10-54 years of age. Based upon the extent of use observed in the Clozaril(R) National Registry, the mortality rate associated with pulmonary embolus was 1 death per 3,450 person-years of use. This rate was about 27.5 times higher than that in the general population of a similar age and gender (95% Confidence Interval; 17.1, 42.2). Deep vein thrombosis has also been observed in association with CLOZARIL therapy. Whether pulmonary embolus can be attributed to CLOZARIL or some characteristic(s) of its users is not clear, but the occurrence of deep vein thrombosis or respiratory symptomatology should suggest its presence.

Hepatitis

Caution is advised in patients using CLOZARIL who have concurrent hepatic disease. Hepatitis has been reported in both patients with normal and pre-existing liver function abnormalities. In patients who develop nausea, vomiting, and/or anorexia during CLOZARIL treatment, liver function tests should be performed immediately. If the elevation of these values is clinically relevant or if symptoms of jaundice occur, treatment with CLOZARIL should be discontinued.

Anticholinergic Toxicity

Eye: CLOZARIL has potent anticholinergic effects and care should be exercised in using this drug in the presence of narrow angle glaucoma.

Gastrointestinal: CLOZARIL use has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, fecal impaction and paralytic ileus *(see ADVERSE REACTIONS).* On rare occasions, these cases have been fatal. Constipation should be initially treated by ensuring adequate hydration, and use of ancillary therapy such as bulk laxatives. Consultation with a gastroenterologist is advisable in more serious cases.

Prostate: CLOZARIL has potent anticholinergic effects and care should be exercised in using this drug in the presence of prostatic enlargement.

Interference with Cognitive and Motor Performance

Because of initial sedation, CLOZARIL may impair mental and/or physical abilities, especially during the first few days of therapy. The recommendations for gradual dose escalation should be carefully adhered to, and patients cautioned about activities requiring alertness.

Use in Patients with Concomitant Illness

Clinical experience with CLOZARIL in patients with concomitant systemic diseases is limited. Nevertheless, caution is advisable in using CLOZARIL in patients with renal or cardiac disease.

Use in Patients Undergoing General Anesthesia

Caution is advised in patients being administered general anesthesia because of the CNS effects of CLOZARIL. Check with the anesthesiologist regarding continuation of CLOZARIL therapy in a patient scheduled for surgery.

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe CLOZARIL:

Patients who are to receive CLOZARIL should be warned about the significant risk of developing agranulocytosis. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat, malaise, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection.
Patients should be informed that CLOZARIL tablets will be made available only through a special program designed to ensure the required blood monitoring in order to reduce the risk of developing agranulocytosis. Patients should be informed that their WBC count and ANC will be monitored as follows:
Weekly blood tests are required for the first 6 months.If acceptable WBC counts and ANCs (WBC >/=3500/mm[3] and ANC >/=2000/mm[3]) have been maintained during the first 6 months of continuous therapy, then WBC counts and ANCs can be monitored every 2 weeks for the next 6 months.Thereafter, if acceptable WBC counts and ANCs have been maintained during the second 6 months of continuous therapy, WBC counts and ANCs can be monitored every 4 weeks.Patients should be informed of the significant risk of seizure during CLOZARIL treatment, and they should be advised to avoid driving and any other potentially hazardous activity while taking CLOZARIL.Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.Patients should be informed that if they miss taking CLOZARIL for more than 2 days, they should not restart their medication at the same dosage, but should contact their physician for dosing instructions.Patients should notify their physician if they are taking, or plan to take, any prescription or over-the-counter drugs or alcohol.Patients should notify their physician if they become pregnant or intend to become pregnant during therapy.Patients should not breast-feed an infant if they are taking CLOZARIL.

Drug Interactions

The risks of using CLOZARIL in combination with other drugs have not been systematically evaluated.

Pharmacodynamic-Related Interactions: The mechanism of CLOZARIL-induced agranulocytosis is unknown;

nonetheless, the possibility that causative factors may interact synergistically to increase the risk and/or severity of bone marrow suppression warrants consideration. Therefore, CLOZARIL should not be used with other agents having a well-known potential to suppress bone marrow function.

Given the primary CNS effects of CLOZARIL, caution is advised in using it concomitantly with other CNS-active drugs or alcohol.

Orthostatic hypotension in patients taking clozapine can, in rare cases (approximately 1 case per 3,000 patients), be accompanied by profound collapse and respiratory and/or cardiac arrest. Some of the cases of collapse/respiratory arrest/cardiac arrest during initial treatment occurred in patients who were being administered benzodiazepines; similar events have been reported in patients taking other psychotropic drugs or even CLOZARIL by itself. Although it has not been established that there is an interaction between CLOZARIL and benzodiazepines or other psychotropics, caution is advised when clozapine is initiated in patients taking a benzodiazepine or any other psychotropic drug.

CLOZARIL may potentiate the hypotensive effects of antihypertensive drugs and the anticholinergic effects of atropine-type drugs. The administration of epinephrine should be avoided in the treatment of drug-induced hypotension because of a possible reverse epinephrine effect.

Pharmacokinetic-Related Interactions: Clozapine is a substrate for many CYP450 isozymes, in particular 1A2, 2D6, and 3A4. The risk of metabolic interactions caused by an effect on an individual isoform is therefore minimized. Nevertheless, caution should be used in patients receiving concomitant treatment with other drugs that are either inhibitors or inducers of these enzymes.

Concomitant administration of drugs known to induce cytochrome P450 enzymes may decrease the plasma levels of clozapine. Phenytoin, nicotine, and rifampin may decrease CLOZARIL plasma levels, resulting in a decrease in effectiveness of a previously effective CLOZARIL dose.

Concomitant administration of drugs known to inhibit the activity of cytochrome P450 isozymes may increase the plasma levels of clozapine. Cimetidine, caffeine, citalopram, ciprofloxacin, and erythromycin may increase plasma levels of CLOZARIL, potentially resulting in adverse effects. Although concomitant use of CLOZARIL and carbamazepine is not recommended, it should be noted that discontinuation of concomitant carbamazepine administration may result in an increase in CLOZARIL plasma levels.

In a study of schizophrenic patients who received clozapine under steady-state conditions, fluvoxamine or paroxetine was added in 16 and 14 patients, respectively. After 14 days of co-administration, mean trough concentrations of clozapine and its metabolites, *N*-desmethylclozapine and clozapine *N*-oxide, were elevated with fluvoxamine by about three-fold compared to baseline concentrations. Paroxetine produced only minor changes in the levels of clozapine and its metabolites. However, other published reports describe modest elevations (less than two-fold) of clozapine and metabolite concentrations when clozapine was taken with paroxetine, fluoxetine, and sertraline. Therefore, such combined treatment should be approached with caution and patients should be monitored closely when CLOZARIL is combined with these drugs, particularly with fluvoxamine. A reduced CLOZARIL dose should be considered.

A subset (3%-10%) of the population has reduced activity of certain drug metabolizing enzymes such as the cytochrome P450 isozyme P450 2D6. Such individuals are referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, the tricyclic antidepressants, and clozapine. These individuals may develop higher than expected plasma concentrations of clozapine when given usual doses. In addition, certain drugs that are metabolized by this isozyme, including many antidepressants (clozapine, selective serotonin reuptake inhibitors, and others), may inhibit the activity of this isozyme, and thus may make normal metabolizers resemble poor metabolizers with regard to concomitant therapy with other drugs metabolized by this enzyme system, leading to drug interaction.

Concomitant use of clozapine with other drugs metabolized by cytochrome P450 2D6 may require lower doses than usually prescribed for either clozapine or the other drug. Therefore, co-administration of clozapine with other drugs that are metabolized by this isozyme, including antidepressants, phenothiazines, carbamazepine, and Type 1C antiarrhythmics (e.g., propafenone, flecainide and encainide), or that inhibit this enzyme (e.g., quinidine), should be

approached with caution.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenic potential was demonstrated in long-term studies in mice and rats at doses approximately 7 times the typical human dose on a mg/kg basis. Fertility in male and female rats was not adversely affected by clozapine. Clozapine did not produce genotoxic or mutagenic effects when assayed in appropriate bacterial and mammalian tests.

Pregnancy Category B

Reproduction studies have been performed in rats and rabbits at doses of approximately 2–4 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to clozapine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and in view of the desirability of keeping the administration of all drugs to a minimum during pregnancy, this drug should be used only if clearly needed.

Nursing Mothers

Animal studies suggest that clozapine may be excreted in breast milk and have an effect on the nursing infant. Therefore, women receiving CLOZARIL should not breast-feed.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of clozapine did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects.

Orthostatic hypotension can occur with CLOZARIL treatment and tachycardia, which may be sustained, has been observed in about 25% of patients taking CLOZARIL *(see BOXED WARNING , Other Adverse Cardiovascular and Respiratory Effects)*. Elderly patients, particularly those with compromised cardiovascular functioning, may be more susceptible to these effects.

Also, elderly patients may be particularly susceptible to the anticholinergic effects of CLOZARIL, such as urinary retention and constipation. *(See PRECAUTIONS , Anticholinergic Toxicity .)*

Dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Other reported clinical experience does suggest that the prevalence of tardive dyskinesia appears to be highest among the elderly, especially elderly women. *(See WARNINGS , Tardive Dyskinesia .)*

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Sixteen percent of 1,080 patients who received CLOZARIL(R) (clozapine) in pre-marketing clinical trials discontinued treatment due to an adverse event, including both those that could be reasonably attributed to CLOZARIL treatment and those that might more appropriately be considered intercurrent illness. The more common events considered to be causes of discontinuation included: CNS, primarily drowsiness/sedation, seizures, dizziness/syncope; cardiovascular, primarily tachycardia, hypotension and ECG changes; gastrointestinal, primarily nausea/vomiting; hematologic, primarily leukopenia/granulocytopenia/agranulocytosis; and fever. None of the events enumerated accounts for more than 1.7% of all discontinuations attributed to adverse clinical events.

Commonly Observed

Adverse events observed in association with the use of CLOZARIL in clinical trials at an incidence of greater than 5% were: central nervous system complaints, including drowsiness/sedation, dizziness/vertigo, headache and tremor; autonomic nervous system complaints, including salivation, sweating, dry mouth and visual disturbances; cardiovascular findings, including tachycardia, hypotension and syncope; and gastrointestinal complaints, including constipation and nausea; and fever. Complaints of drowsiness/sedation tend to subside with continued therapy or dose reduction. Salivation may be profuse, especially during sleep, but may be diminished with dose reduction.

Incidence in Clinical Trials

The following table enumerates adverse events that occurred at a frequency of 1% or greater among CLOZARIL patients who participated in clinical trials. These rates are not adjusted for duration of exposure.

Treatment-Emergent Adverse Experience Incidence Among Patients Taking CLOZARIL(R) (clozapine) in Clinical Trials (excluding the InterSePT(TM) Study) (N=842) (Percentage of Patients Reporting)

Body System Adverse Event[a]	Percent
Central Nervous System	
Drowsiness/Sedation	39
Dizziness/Vertigo	19
Headache	7
Tremor	6
Syncope	6
Disturbed Sleep/Nightmares	4
Restlessness	4
Hypokinesia/Akinesia	4
Agitation	4
Seizures (Convulsions)	3[b]
Rigidity	3
Akathisia	3
Confusion	3
Fatigue	2
Insomnia	2
Hyperkinesia	1
Weakness	1
Lethargy	1
Ataxia	1
Slurred Speech	1
Depression	1
Epileptiform Movements/Myoclonic Jerks	1
Anxiety	1
Cardiovascular	
Tachycardia	25[b]
Hypotension	9
Hypertension	4
Chest Pain/Angina	1
ECG Change/Cardiac Abnormality	1
Gastrointestinal	

Treatment-Emergent Adverse Experience Incidence Among Patients Taking CLOZARIL(R) (clozapine) in Clinical Trials (excluding the InterSePT(TM) Study) (N=842) (Percentage of Patients Reporting)	
Constipation	14
Nausea	5
Abdominal Discomfort/Heartburn	4
Nausea/Vomiting	3
Vomiting	3
Diarrhea	2
Liver Test Abnormality	1
Anorexia	1
Urogenital	
Urinary Abnormalities	2
Incontinence	1
Abnormal Ejaculation	1
Urinary Urgency/Frequency	1
Urinary Retention	1
Autonomic Nervous System	
Salivation	31
Sweating	6
Dry Mouth	6
Visual Disturbances	5
Integumentary (Skin)	
Rash	2
Musculoskeletal	
Muscle Weakness	1
Pain (Back, Neck, Legs)	1
Muscle Spasm	1
Muscle Pain, Ache	1
Respiratory	
Throat Discomfort	1
Dyspnea, Shortness of Breath	1
Nasal Congestion	1
Hemic/Lymphatic	
Leukopenia/Decreased WBC/Neutropenia	3
Agranulocytosis	1[b]
Eosinophilia	1
Miscellaneous	
Fever	5
Weight Gain	4
Tongue Numb/Sore	1

[a] Events reported by at least 1% of CLOZARIL patients are included.
[b] Rate based on population of approximately 1,700 exposed during pre-market clinical evaluation of CLOZARIL.

The following table enumerates adverse events that occurred at a frequency of 10% for either treatment group in patients who took at least 1 dose of study medication during their participation in InterSePT, which was an adequate and well-controlled 2-year study evaluating the efficacy of CLOZARIL relative to Zyprexa in reducing the risk of emergent suicidal behavior in patients with schizophrenia or schizoaffective disorder. These rates are not adjusted for duration of exposure.

Treatment-Emergent Adverse Experience Incidence[1] Among Patients Taking CLOZARIL(R) (clozapine) or Zyprexa(R) (olanzapine) in the InterSePT(TM) Study (Percentage of Patients Reporting)

	CLOZARIL(R) N=479 % Reporting	Zyprexa(R) N=477 % Reporting
Adverse Events		
Salivary hypersecretion	48%	6%
Somnolence	46%	25%
Weight increased	31%	56%
Dizziness (Excluding Vertigo)	27%	12%
Constipation	25%	10%
Insomnia NEC	20%	33%
Nausea	17%	10%
Vomiting NOS	17%	9%
Dyspepsia	14%	8%

[1] AEs are listed by frequency in CLOZARIL group, and included in the table are those for which the risk ratio of CLOZARIL over Zyprexa or of Zyprexa over CLOZARIL was greater than 1.5.
NEC - not elsewhere classified
NOS - not otherwise specified

Other Events Observed During the Pre-marketing Evaluation of CLOZARIL(R) (clozapine)

This section reports additional, less frequent adverse events which occurred among the patients taking CLOZARIL in clinical trials. Various adverse events were reported as part of the total experience in these clinical studies; a causal relationship to CLOZARIL treatment cannot be determined in the absence of appropriate controls in some of the studies. The table above enumerates adverse events that occurred at a frequency of at least 1% of patients treated with CLOZARIL. The list below includes all additional adverse experiences reported as being temporally associated with the use of the drug which occurred at a frequency less than 1%, enumerated by organ system.

Central Nervous System: loss of speech, amentia, tics, poor coordination, delusions/hallucinations, involuntary movement, stuttering, dysarthria, amnesia/memory loss, histrionic movements, libido increase or decrease, paranoia, shakiness, Parkinsonism, and irritability.

Cardiovascular System: edema, palpitations, phlebitis/thrombophlebitis, cyanosis, premature ventricular contraction, bradycardia, and nosebleed.

Gastrointestinal System: abdominal distention, gastroenteritis, rectal bleeding, nervous stomach, abnormal stools, hematemesis, gastric ulcer, bitter taste, and eructation.

Urogenital System: dysmenorrhea, impotence, breast pain/discomfort, and vaginal itch/infection.

Autonomic Nervous System: numbness, polydipsia, hot flashes, dry throat, and mydriasis.

Integumentary (Skin): pruritus, pallor, eczema, erythema, bruise, dermatitis, petechiae, and urticaria.

Musculoskeletal System: twitching and joint pain.

Respiratory System: coughing, pneumonia/pneumonia-like symptoms, rhinorrhea, hyperventilation, wheezing,