Archives of Family Medicine

Devoted to strengthening the science, practice, and art of family medicine.

• The best original research in the specialty.
• Clinically practical, academically sound.
• Published every other month (six times in 1997).
• More content in each issue.
• Better paper stock and binding method.
• Easier to read and refer to, again and again.
ASTHMA AND PANIC DISORDER

ARE SYMPTOMS OF ANXIETY AND DEPRESSION RISK FACTORS FOR HYPERTENSION?

PERFORMANCE OF GASTROINTESTINAL TRACT ENDOSCOPY BY PRIMARY CARE PHYSICIANS

HOW TO SUBMIT A SPECIMEN FOR CUTANEOUS PATHOLOGY ANALYSIS

THE RELATIONSHIP OF SELF-ESTEEM TO THE HEALTH-RELATED BEHAVIORS OF THE PATIENTS OF A PRIMARY CARE CLINIC

PREFERENCES OF HUSBANDS AND WIVES FOR PROSTATE CANCER SCREENING
Put the sting on the bugs, not the baby blues.

POLYTRIM® Solution eradicates the most common causative pathogens of bacterial conjunctivitis. And it has proven efficacy against H. influenzae.¹

Eliminating H. flu is critical, because it causes 3-4 times more cases of bacterial conjunctivitis in children than any other ocular pathogen.²

Yet for all its bactericidal activity, POLYTRIM® is safe and effective for children 2 months and over. It’s comfortable on instillation, and contains no neomycin or sulfa.

All good reasons why POLYTRIM® makes an excellent pinkeye solution. Especially for those baby blues.

Polytrim®
Ophthalmic Solution Sterile
(trimethoprim sulfate 0.1%, polymyxin B sulfate 10,000 units/mL)

For bacterial conjunctivitis due to susceptible strains of Haemophilus influenzae, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Streptococcus viridans, and Pseudomonas aeruginosa.³

³Efficacy for this organism was studied in fewer than 10 infections.

NOTE: The most frequent adverse reaction is local irritation consisting of increased redness, burning, stinging, or itching. Not indicated for the treatment of ophthalmia neonatorum.

Please see adjacent page for references and brief prescribing information.

It Kills Pinkeye With Kindness

©1995 Allergan, Inc., Irvine, CA 92715
POLYTRIM® Ophthalmic Solution Sterile
(trimethoprim sulfate 0.1% and polymyxin B sulfate 10,000 units/mL)

INDICATIONS AND USAGE: POLYTRIM® Ophthalmic Solution is indicated in the treatment of surface ocular bacterial infections, including acute bacterial conjunctivitis, and blepharocconjunctivitis, caused by susceptible strains of the following microorganisms: Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Streptococcus viridans, Haemophilus influenzae, and Pseudomonas aeruginosa. * Efficacy for this organism in this organ system was studied in fewer than 10 infections.

CONTRAINDICATIONS: POLYTRIM® Ophthalmic Solution is contraindicated in patients with known hypersensitivity to any of its components.

WARNINGS: NOT FOR INJECTION INTO THE EYE. If a sensitivity reaction to POLYTRIM® occurs, discontinue use. POLYTRIM® Ophthalmic Solution is not indicated for the prophylaxis or treatment of ophtalmia neonatorum.

PRECAUTIONS:
General: As with other antimicrobial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated.

Information for Patients: Avoid contaminating the applicator tip with material from the eye, fingers, or other source. This precaution is necessary if the sterility of the drops is to be maintained. If redness, irritation, swelling or pain persists or increases, discontinue use immediately and contact your physician. Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis: Long-term studies in animals to evaluate carcinogenic potential have not been conducted with polymyxin B sulfate or trimethoprim. Mutagenesis: Trimethoprim was demonstrated to be non-mutagenic in the Ames assay. In studies at two laboratories, no chromosomal damage was detected in cultured Chinese hamster ovary cells at concentrations approximately 500 times human plasma levels after oral administration; at concentrations approximately 1000 times human plasma levels after oral administration in these same cells a low level of chromosomal damage was induced at one of the laboratories. Studies to evaluate mutagenic potential have not been conducted with polymyxin B sulfate. Impairment of Fertility: Polymyxin B sulfate has been reported to impair the motility of equine sperm, but its effects on male or female fertility are unknown. No adverse effects on fertility or general reproductive performance were observed in rats given trimethoprim in oral dosages as high as 70 mg/kg/day for males and 14 mg/kg/day for females. Pregnancy: Teratogenic Effects: Pregnancy Category C. Animal reproductive studies have not been conducted with polymyxin B sulfate. It is not known whether polymyxin B sulfate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

Trimethoprim has been shown to be teratogenic in the rat when given in oral doses 40 times the human dose. In some rabbit studies, the overall increase in fetal loss (dead and resorbed and malformed conceptuses) was associated with oral doses 6 times the human therapeutic dose. While there are no large well-controlled studies on the use of trimethoprim in pregnant women, Brumfitt and Pursell, in a retrospective study, reported the outcome of 186 pregnancies during which the mother received either placebo or oral trimethoprim in combination with sulfamethoxazole. The incidence of congenital abnormalities was 4.5% (3 of 66) in those who received placebo and 3.3% (4 of 120) in those receiving trimethoprim and sulfamethoxazole. There were no abnormalities in the 10 children whose mothers received the drug during the first trimester. In a separate survey, Brumfitt and Pursell also found no congenital abnormalities in 35 children whose mothers had received oral trimethoprim and sulfamethoxazole at the time of conception or shortly thereafter. Because trimethoprim may interfere with folic acid metabolism, trimethoprim should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: The oral administration of trimethoprim to rats at a dose of 70 mg/kg/day commencing with the last third of gestation and continuing through parturition and lactation caused no deleterious effects on gestation or pup growth and survival. Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when POLYTRIM® Ophthalmic Solution is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 2 months have not been established (see WARNINGS).

ADVERSE REACTIONS: The most frequent adverse reaction to POLYTRIM® Ophthalmic Solution is local irritation consisting of increased redness, burning, stinging, and/or itching. This may occur on instillation, within 48 hours, or at any time with extended use. There are also multiple reports of hypersensitivity reactions consisting of lid edema, itching, increased redness, tearing, and/or circumocular rash. Photosensitivity has been reported in patients taking oral trimethoprim.


©1995 Allergan, Inc., Irvine, CA 92715
SPECIAL SELECTION

Clinical Picture 15
Walter W. Tunnessen, Jr, MD; Howard Markel, MD, PhD

LIVING IN MEDICINE

Daniel’s Fees 17
Joel Lazar, MD

LETTERS TO THE EDITOR

Association of Vaginal Ultrasound and Urinary Tract Infection 18
Steven G. Hammer, MD

Running and Its Effect on Family Life: A Follow-up of Spouses’ Perceptions 18
Daniel S. Fick, MD; Stephen J. Goff, PhD; Robert A. Oppliger, PhD

ORIGINAL CONTRIBUTIONS

Asthma and Panic Disorder 20
Karen B. Schmaling, PhD; Jon Bell, MD

Community Preceptors’ Views of a Required Third-Year Family Medicine Clerkship 25
Donald O. Kollisch, MD; Pamela York Frasier, MSPH; Lisa Slatt, MEd; Marie Storaasli, MS

Primary Care Physicians’ Practice Patterns and Diabetic Retinopathy: Current Levels of Care 29
Stephanie Kakos Kraft, MPH; David G. Marrero, PhD; Emmanuel N. Lazaridis, PhD; Naomi Fineberg, PhD; Chunfu Qiu, PhD; Charles M. Clark, Jr, MD

EDITORIAL

Preventive Health Care for Diabetics: A Realistic Vision 38
Richard C. Wender, MD

ORIGINAL CONTRIBUTION

Are Symptoms of Anxiety and Depression Risk Factors for Hypertension? Longitudinal Evidence From the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study 43
Bruce S. Jonas, PhD; Peter Franks, MD; Deborah D. Ingram, PhD

American Medical Association
Physicians dedicated to the health of America
independence

Liberating
patients
from arthritis
pain.

All in pursuit of the
freedom of
movement.

Two caplets, once a day*

DAYPRO®
(oxaprozin)
600-mg
caplets

Daylong Confidence. Proactive Control.

DAYPRO is indicated for the treatment of the signs and symptoms of OA and RA.

Usual adult dosage is 1200 mg (two 600-mg caplets) once a day. For osteoarthritis patients of low body weight or with milder disease, an initial dosage of one 600-mg caplet once a day, or an optional one-time loading dose of 1200 mg, may be appropriate. Dosage should be individualized to the lowest effective dose; the maximum recommended total daily dosage is 1800 mg or 26 mg/kg, whichever is lower, in divided doses.

Contraindicated in patients with hypersensitivity to DAYPRO or in individuals with nasal polyps, angioedema, or bronchospastic reactivity to aspirin or other NSAIDs. Severe and occasionally fatal asthmatic and anaphylactic reactions to NSAIDs have been reported; there have been rare reports of anaphylaxis with DAYPRO. As with other NSAIDs, the most frequently reported adverse reactions were related to the GI tract. In patients treated chronically with NSAID therapy, serious GI toxicity, such as bleeding, ulceration, and perforation, can occur. Severe renal and hepatic reactions have been reported. There may be a risk of fatal hepatitis with oxaprozin, such as has been seen with other NSAIDs.

Please see brief summary of prescribing information on adjacent page.
INDICATIONS AND USAGE: Daypro is indicated for the treatment of the signs and symptoms of OA and RA.

CONTRAINdications: Hypersensitivity to oxaprozin or any of its components or in individuals with a history of aspirin hypersensitivity should be considered before the use of Daypro. Patients with a history of aspirin-induced asthma and/or anaphylaxis should not receive Daypro.

WARNINGS: RISK OF GASTROINTESTINAL (GI) TRACT BLEEDING, AND PERFUSION PROBLEMS: GI tract bleeding or perforation, which can be fatal, occurs at a higher rate with Daypro than with other NSAIDs. Patients should be aware of the risk of serious GI tract bleeding or perforation and should report any symptoms of such bleeding to their healthcare provider. Patients with a history of peptic ulcer disease should be monitored closely for signs of bleeding or perforation.

Photosensitivity: Daypro has been associated with photosensitivity reactions, including rash and phototoxicity. Patients should be advised to protect themselves from sun exposure and to use protective clothing and sunscreen.

NSAIDs, including Daypro, can cause anuria and renal failure, especially in elderly patients and those with fluid retention, dehydration, or heart failure. Patients should be advised to report any signs of fluid retention, such as weight gain, swelling, or shortness of breath.

Precautions: General: Hepatic effects: As with other NSAIDs, borderline elevations of enzymes may occur. The abnormality is usually undetectable or self-limited. If hepatic dysfunction progresses, remain essentially unchanged, or resolve with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times above normal) elevations in transaminase levels have been observed in some patients receiving Daypro, but in most cases, the transaminase elevations were less than 3 times normal. Should a patient experience any increase in alanine aminotransferase (ALT), the dosage of Daypro should be reduced or the medication discontinued.

Photosensitivity: Undesirable photosensitivity reactions have been reported with Daypro therapy. This reaction has been associated with increased skin pigmentation or rash. Patients should be instructed to protect themselves from sun exposure and to use protective clothing and sunscreen.

NSAIDs, including Daypro, can cause fluid retention, especially in elderly patients and those with heart failure. Patients should be advised to report any signs of fluid retention, such as weight gain, swelling, or shortness of breath.

Cardiac hypertrophy has been reported in animal studies with Daypro. However, the clinical significance of this finding is not known.

Drug Abuse and Dependence: Daypro is not a narcotic drug. Usual desirable analgesic effects are indicated that Daypro has no known addiction potential in humans.

OVERDOSAGE: No patient experienced either an accidental or intentional overdosage of Daypro in the clinical trials of the drug. Symptoms following acute overdose with other NSAIDs are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain and are generally reversible with supportive care. Gastrointestinal bleeding and coma have occurred following Daypro overdose. Hypertension, acute renal failure, and respiratory depression are rare. Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Gouty arthritis and related symptoms can be treated with standard therapy. Patients with acute renal failure should be evaluated for the need for dialysis. If Daypro administration was initiated within 10–15 hours of the acute toxicity, dialysis might be considered. Patients with severe renal failure or those who are only partially exposed to the drug may benefit from dialysis. The use of dialysis is generally not feasible in patients who have received Daypro for a longer period of time.

Drug Interactions: St. John's wort has been reported to increase plasma concentrations of concomitantly administered drugs. The clinical consequences of this interaction are not known. Daypro is not recommended for use in patients taking St. John's wort.

BRIEF SUMMARY — DAYPRO® (oxaprozin) 600-mg caplets
Before prescribing please see full prescribing information. Daypro is a non-narcotic drug. Usual desirable analgesic effects are indicated that Daypro has no known addiction potential in humans.

5/9/56 P961DA2668V
Address medical inquiries to: G.D. Searle
Healthcare Information Services
5200 Old Orchard Road
Skokie, IL 60077

SEARLE
G.D. Searle & Co.
Box 5110, Chicago, IL 60698 USA
AUTHOR RESPONSIBILITY FORM

AUTHORSHIP RESPONSIBILITY, FINANCIAL DISCLOSURE, AND ASSIGNMENT OF COPYRIGHT

Each author must read and sign (1) the statement on authorship responsibility; (2) the statement on financial disclosure; and (3) either the statement on copyright transfer or the statement on federal employment. If necessary, photocopy this document to distribute to coauthors for their signatures. Please return all copies to the address below.

1. Authorship Responsibility

I have participated sufficiently in the conception and design of this work or the analysis and interpretation of the data (when applicable), as well as the writing of the manuscript, to take public responsibility for it. I believe the manuscript represents valid work. I have reviewed the final version of the manuscript and approve it for publication.

Author(s) Signature(s)

Neither this manuscript nor one with substantially similar content under my (our) authorship has been published or is being considered for publication elsewhere, except as described in an attachment.

Furthermore, I attest that I shall produce the data upon which the manuscript is based for examination by the editors or their assignees should they request it.

Date Signed

2. Financial Disclosure

I certify that I have no affiliation with or financial involvement in any organization or entity with a direct financial interest in the subject matter or materials discussed in the manuscript (eg, employment, consultancies, stock ownership, honoraria), except as disclosed in an attachment.

Any financial project support of this research is identified in an acknowledgment in the manuscript.

Date Signed

3. Copyright

In compliance with the Copyright Revision Act of 1976, effective January 1, 1978, the American Medical Association (AMA), in consideration of taking further action in reviewing and editing your submission, requests that each author sign a copy of this form before manuscript review can proceed. Such signature shall evidence the mutual understanding between the AMA and the undersigned author(s) thereby transferring, as

Author(s) Signature(s)

signing, or otherwise conveying all copyright ownership, including any and all rights incidental thereto, exclusively to the AMA.

In consideration of the action of the AMA in reviewing and editing this submission, the author(s) undersigned hereby transfer(s), or otherwise convey(s) all copyright ownership to the AMA in the event that such work is published by the AMA.

Date Signed

US Federal Employees: If you are an employee of the US federal government, please sign the following statement: I was an employee of the US federal government when this work was conducted and prepared for publication; therefore, it is not protected by the Copyright Act and there is no copyright, thus ownership cannot be transferred.

Author(s) Signature(s)

Date Signed

Return the original signed form to Marjorie A. Bowman, MD, MPA, Editor, Archives of Family Medicine, University of Pennsylvania Health System, 1126 Penn Tower, 399 S 34th St, Philadelphia, PA 19104-4385. Retain 1 copy for your files. (Photocopies may be made as needed.) See page 7 for complete Instructions for Authors.
Saunders MANUAL OF MEDICAL PRACTICE
Your master key to effective patient management! A user-friendly outline format speeds you to the symptoms, diagnosis, and treatment of more than 318 diseases and disorders. Features more than 60 office procedures.
Edited by Robert E. Rakel, MD; with 413 contributors. 1996. 1287 pp. 285 figs. (118 in 2 color), 103 tables. $197.50. Order #W6192-5.

Cecil TEXTBOOK OF MEDICINE, 20th Edition CD-ROM
Access Cecil TEXTBOOK OF MEDICINE, 20th Edition with the speed, power, and convenience of a CD-ROM!

TEXTBOOK OF FAMILY PRACTICE, 5th Edition
"No single textbook...better addresses the needs of a family practitioner. A worthwhile investment." (Family Medicine, review of last edition)
Sometimes you just need to know now. And thanks to the new Archives of Family Medicine World Wide Web site, now is just a click away.

Locating practical clinical information has never been easier. Or faster. Pinpoint current and past Archives articles, access informative summaries and abstracts, review full tables of contents, and more.

Whether you need instant information or want to make better use of your printed journal, you’ll find our Website just what you ordered.

http://www.ama-assn.org

CLICK ON ARCHIVES JOURNALS TODAY
Working together to improve community health and quality care through... **Provider Sponsored Organizations (PSOs)**

To find out how... attend the first AMA/AHA joint educational event on December 6 in Atlanta. The program is part of the 1996 Interim AMA Organized Medical Staff Section Assembly Meeting.

**The Program**...
- Learn to build strong physician-hospital partnerships vital to survival and success in health care today!
- Get practical information on what PSOs can mean to patients, communities and you!
- Discover the advantages and differences when hospitals and physicians take the lead!
- Hear from physician and hospital leaders...PSO success stories!

**The Cost**... is free!

**The Speakers**...
Dartmouth health policy expert John E. Wennberg, MD, MPH, will give you the big picture. His *Dartmouth Atlas of Health Care* shows how and where care is provided in America.

PSO leaders K. James Ehlen, MD, Allina Health System in Minneapolis, and Stewart H. Gleischman, MD, Health Source Medical Group in Los Angeles, along with AMA and AHA experts will chart your path to PSOs.

**Come experience the new synergy.** Plan now to attend. To register call 800 AMA-3211 and ask for the Department of Organized Medical Staff Services.

*The AMA is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.*

The AMA designates this continuing medical education activity for up to 3 credit hours in Category 1 of the Physician’s Recognition Award.

American Medical Association
Physicians dedicated to the health of America

American Hospital Association
New!
American Medical Association
Complete Guide to Women's Health

For Every Stage of Every Woman's Life.
The most in-depth, up-to-date book ever for protecting your health and well being. Valuable advice on hundreds of important women's health topics. A special book-within-a-book, What You Can Do for Your Body Now, highlights health priorities for women in four age groups.

More than 700 illustrations, photographs, charts, and graphs; full-color atlas of the body; complete index for easy reference — 768 information-filled pages in all. From America's most respected authority on health.

Order Your Copy Today!
Call 800 621-8335.
Mention priority code ACE.

Visa, MasterCard, American Express/Optima accepted
Order #: OP840996ACE
Price: $39.95

Applicable state sales tax and shipping and handling added. Satisfaction guaranteed.
REFERENCES

CONTRAINDICATIONS

CARDIZEM® CD is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker; (2) patients with second- or third-degree AV block, except in the presence of a functioning ventricular pacemaker; (3) patients with hypotension (less than 90/50 mm Hg), or (4) patients who have had hypersensitivity to the drug and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

1. Cardiac Conduction. CARDIZEM® CD prolongs AV node refractory period and may slow the conduction of non-sustained ventricular recovery time, except in patients with sick sinus syndrome. This effect may vary among patients (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3290 patients or 0.4%). Concomitant use of drugs known to prolong the QT interval and affect cardiac conduction is contraindicated in patients with sick sinus syndrome. A patient with Poincet's syndrome and a prolonged QT interval is at risk for cardiac arrhythmias. A patient with Poincet's syndrome should be carefully monitored for evidence of cardiac arrhythmias. (See ADVERSE REACTIONS and PRECAUTIONS sections.)

2. Constrictive Heart Failure. Although digoxin has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in man have shown no significant effect on left or right ventricular function in patients without significant constrictive or restrictive ventricular function. (See WARNINGS and PRECAUTIONS sections.)

3. Cardiac Failure. Mild elevations of transaminases with and/or concomitant elevations in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued digoxin therapy. In rare instances, significant elevations and/or bilirubin have been observed. (See WARNINGS and PRECAUTIONS sections.)


5. Acute Hepatic Injury. Mild elevations of transaminases and alkaline phosphatase have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued digoxin therapy. In rare instances, significant elevations and/or bilirubin have been observed. (See WARNINGS and PRECAUTIONS sections.)

6. Cardiac Failure. Mild elevations of transaminases with and/or concomitant elevations in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued digoxin therapy. In rare instances, significant elevations and/or bilirubin have been observed. (See WARNINGS and PRECAUTIONS sections.)

7. Cardiac Failure. Mild elevations of transaminases with and/or concomitant elevations in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued digoxin therapy. In rare instances, significant elevations and/or bilirubin have been observed. (See WARNINGS and PRECAUTIONS sections.)

8. Cardiac Failure. Mild elevations of transaminases with and/or concomitant elevations in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued digoxin therapy. In rare instances, significant elevations and/or bilirubin have been observed. (See WARNINGS and PRECAUTIONS sections.)

PRECAUTIONS

General

CARDIZEM® CD (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters of renal and hepatic function should be monitored at regular intervals. The dose should be used with caution in patients with impaired renal or hepatic function. In subsequent and chronic and dog studies designed to produce toxic effects, high doses of diltiazem were associated with hepatic damage. In special subject hepatic studies, oral doses of 1500 mg/kg and higher were associated with hepatic and/or renal changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatologic events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM® CD. However, skin eruptions progressing to erythema multiforme and/or toxic epidermal necrolysis have also been reported (see ADVERSE REACTIONS section).

Drug Interactions

Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM® CD concomitantly with other agents known to affect cardiac conduction and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction, and this may occur in patients taking beta-blockers or digoxin concomitantly with CARDIZEM® CD. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM® CD undergoes biotransformation by cytochrome P-450 mixed function oxidases. Co-administration of CARDIZEM® CD with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Especially in patients with renal and/or hepatic impairment, dosage adjustment of disulfiram, certain antacids, cimetidine, and doses of pimozide should be considered. (See WARNINGS.)

ADVERSE REACTIONS

Serious, adverse effects have not been noted in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The following table presents the most common adverse reactions reported in placebo-controlled angina and hypertension trials in patients receiving CARDIZEM® CD (diltiazem HCl) capsules.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Cardizem CD</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>5.4%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3.0%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>3.3%</td>
<td>3.3%</td>
</tr>
<tr>
<td>AV Block First Degree</td>
<td>1.7%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Edema</td>
<td>2.6%</td>
<td>2.6%</td>
</tr>
<tr>
<td>ECG Abnormality</td>
<td>1.6%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Urticaria</td>
<td>1.6%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Rashes</td>
<td>1.6%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1.6%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Other</td>
<td>1.6%</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

In clinical trials of CARDIZEM® CD, patients, and CARDIZEM® SR capsules involving over 3200 patients, the most common side effects (greater than 5%) were headache (4.6%), dizziness (3.5%), nausea (3.5%), edema (2.6%), and first-degree AV block (2.4%). Bradycardia (1.7%), flushing (1.4%), and rash (1.4%) were also reported.

In addition, the following events were reported infrequently (less than 1%) in patients or hypertension trials:

Cardiovascular: Angina, arrhythmia, AV block (second- or third), bundle branch block, congestive heart failure, ECG abnormalities, hypotension, palpitations, syncope, tachycardia, ventricular extrasystole

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, personality change, somnolence, tremor, transverse myelitis, anorexia, constipation, diarrhea, dry mouth, dysphasia, dyspnea, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hepatic warnings), thirst, vomiting, weight loss

Dermatologic: Pustules, acne, dermatitis, fever, urticaria

Other: Amyloidosisis, arrhythmia, dermatitis, dyspnea, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, ophthalmopathy, palmar erythema, pruritus, rash, rhinitis, sexual disorders, extrapyramidal symptoms, gingival hyperplasia, hematologic anemia, increased blood pressure, increased sweating, nausea, paroxysmal atrial fibrillation, retinopathy, skin eruptions, weight loss, myoclonic twitching, events such as myocardial infarction have been observed which are not readily distinguishable from natural history of the disease in these patients. A number of well-documented cases of generalized rash, some characterized as leukocytoclastic vasculitis, have been reported. However, a definitive relationship of these events and CARDIZEM® CD therapy is yet to be established.

Prescribing Information as of July 1995

Hoechst Marion Roussel, Inc.
Kanata, ON, M4D 1J3 USA

Hoechst Marion Roussel

Hoechst Marion Roussel, Inc. - Kansas City, MO 64137 USA
cod00759

Hoechst Marion Roussel


968410101 ©1996, Hoechst Marion Roussel, Inc. 065767
A UNIQUE HEMODYNAMIC AND SAFETY PROFILE DIFFERENT FROM DIHYDROPYRIDINES

Effective 24-hour control of hypertension or angina
- Reduces blood pressure with no reflex tachycardia
- Increases exercise tolerance, reduces vasospasm, and decreases heart rate in angina

Well tolerated control regardless of age or gender
- A side-effect discontinuation rate comparable to placebo
- Most commonly reported side effects are headache (5.4%), bradycardia (3.3%), first-degree AV block (3.3%), dizziness (3.0%), edema (2.6%), ECG abnormality (1.6%), and asthenia (1.8%)

True 24-hour control from a unique patented delivery system
- No other diltiazem is therapeutically equivalent to Cardizem CD

*Cardizem CD is a benzothiazepine calcium channel blocker.
† In clinical trials with Cardizem CD.
‡ FDA does not, at this time, consider other diltiazems to be therapeutically equivalent because bioequivalence has not been demonstrated through appropriate studies.
* Please see brief summary of prescribing information on adjacent page.

FOR HYPERTENSION OR ANGINA

ONCE-A-DAY CARDIZEM® CD
(diltiazem HCl) 120-, 180-, 240-, 300-mg Capsules

No other diltiazem is therapeutically equivalent
No other diltiazem is therapeutically equivalent.

The following table presents the most common adverse reactions in patients receiving CARDIZEM CD up to 360 mg with rates in placebo patients shown for comparison.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Cardizem CD</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>5.4%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3.0%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>3.3%</td>
<td>3.5%</td>
</tr>
<tr>
<td>AV Block First Degree</td>
<td>3.0%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Edema</td>
<td>2.0%</td>
<td>1.3%</td>
</tr>
<tr>
<td>ECG Abnormality</td>
<td>2.3%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1.8%</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

In clinical trials of CARDIZEM CD capsules, CARDIZEM tablets, and CARDIZEM SR capsules involving over 2,000 patients, the most common events (ie, greater than 1%) were edema (4.6%), headache (4.6%), dizziness (3.5%), asthenia (2.8%), first-degree AV block (2.4%), bradycardia (1.7%), flushing (1.4%), nausea (1.4%), and rash (1.2%). In addition, the following events were reported infrequently (less than 1%) in angina or hypertension trials:

- Cardiovascular: Angina, arrhythmia, AV block (second- or third-degree), bundle branch block, congestive heart failure, ECG abnormalities, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles
- Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dyspepsia, nausea, mild elevations of bilirubin, SGOT, SGPT, and alkaline phosphatase, flatulence, fecal incontinence
- Cutaneous: Acne, rash, pruritus, urticaria

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hypergammaglobulinemia, hyperuricemia, impotence, muscle cramps, nasal congestion, ophthalmia, osteoarthritic pain, polynuropathy, sexual difficulties

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: allergic reactions, alopecia, angioneurotic edema (including facial or periorbital edema), arthralgia, erythema multiforme (including Stevens-Johnson syndrome, toxic epidermal necrolysis), exfoliative dermatitis, extrapyramidal symptoms, pigment hyperplasia, hypothermia, anemia, alopecia, nausea, vomiting, weight increase.

Dermatological: Petechiae, photosensitivity, pruritus, urticaria

References:

Hoechst Marion Roussel, Inc.

Kansas City, MO 64137 USA

A member of the Hoechst Group

Hoechst Marion Roussel

Hoechst Marion Roussel, Inc. 605760

6948301 ©1996, Hoechst Marion Roussel, Inc.
Benefits of a Non-Dihydropyridine CCB

A UNIQUE HEMODYNAMIC AND SAFETY PROFILE DIFFERENT FROM DIHYDROPYRIDINES

Effective 24-hour control of hypertension or angina
- Reduces blood pressure with no reflex tachycardia
- Increases exercise tolerance, reduces vasospasm, and decreases heart rate in angina

Well tolerated control regardless of age or gender
- A side-effect discontinuation rate comparable to placebo
- Most commonly reported side effects are headache (5.4%), bradycardia (3.3%), first-degree AV block (3.3%), dizziness (3.0%), edema (2.6%), ECG abnormality (1.6%), and asthenia (1.8%)

True 24-hour control from a unique patented delivery system
- No other diltiazem is therapeutically equivalent to Cardizem CD

*Cardizem CD is a benzothiazepine calcium channel blocker.
† In clinical trials with Cardizem CD.
‡ FDA does not, at this time, consider other diltiazems to be therapeutically equivalent because bioequivalence has not been demonstrated through appropriate studies.

Please see brief summary of prescribing information on adjacent page.

FOR HYPERTENSION OR ANGINA

ONCE-A-DAY CARDIZEM® CD
(diltiazem HCl) 120-, 180-, 240-, 300-mg Capsules

No other diltiazem is therapeutically equivalent

96483401  ©1996, Hoechst Marion Roussel, Inc.  0657E6