

A Little Means A Lot To The Older Hypertensive

Comparable antihypertensive efficacy to 2.5 mg^{1*} with the safety profile of a lower once-daily dose



Favorable metabolic profile[†]—no adverse effect on lipids; only 2% incidence of clinical hypokalemia[‡]

Safe and effective for step-down therapy

Side-effect profile compatible with other antihypertensive agents

LOZOL 1.25 mg once daily is now the recommended starting dose for indapamide in hypertension

LOW-DOSE ONCE-DAILY
LOZOL[®] 1.25 MG
INDAPAMIDE TABLETS

* In patients with mild or moderate hypertension, a 4-week, single-blind placebo washout period was followed by an 8-week, open-label treatment period with LOZOL 2.5 mg. Patients responding to LOZOL 2.5 mg entered an 8-week, double-blind, randomized treatment period with either LOZOL 2.5 mg or LOZOL 1.25 mg. Treatment success was defined as a decrease in supine diastolic blood pressure to 90 mm Hg or less by week 8 of the double-blind period.

† Because of the diuretic effects of LOZOL 1.25, changes in certain electrolytes and blood chemistries can occur. Serum electrolytes and blood chemistries should therefore be monitored.

‡ 19.6% of patients had values less than 3.4 mEq/L. Only 7.5% had potassium levels below 3.2 mEq/L and less than 1% fell below 3.0 mEq/L. Metabolic changes at higher doses of indapamide may be greater.

As in all step-down therapy, the patient should be monitored for maintenance of blood pressure control.

Please see brief summary of prescribing information below.

LOZOL[®] (indapamide) 1.25 mg and 2.5 mg tablets
BRIEF SUMMARY

INDICATIONS: LOZOL (indapamide) is indicated for the treatment of hypertension, alone or in combination with other antihypertensive drugs, and for the treatment of salt and fluid retention associated with congestive heart failure.

Use and Pregnancy: See PRECAUTIONS.

CONTRAINDICATIONS: Anuria, hypersensitivity to indapamide or other sulfonamide-derived drugs.

WARNINGS: Infrequent cases of severe hyponatremia, accompanied by hypokalemia, have been reported with 2.5 mg and 5.0 mg indapamide primarily in elderly females. Symptoms were reversed by electrolyte replenishment. Hyponatremia considered possibly clinically significant (<125 mEq/L) has not been observed in clinical trials with the 1.25 mg dosage (see PRECAUTIONS). Hypokalemia occurs commonly with diuretics (see ADVERSE REACTIONS, hypokalemia), and electrolyte monitoring is essential. In general, diuretics should not be given with lithium.

PRECAUTIONS: Perform serum electrolyte determinations at appropriate intervals, especially in patients who are vomiting excessively or receiving parenteral fluids, in patients subject to electrolyte imbalance, or in patients on a salt-restricted diet. In addition, patients should be observed for clinical signs of fluid or electrolyte imbalance, such as hyponatremia, hypochloremic alkalosis, or hypokalemia. The risk of hypokalemia secondary to diuresis and natriuresis is increased with larger doses, with brisk diuresis, with severe orthostasis, and with concomitant use of corticosteroids or ACTH. Interference with adequate oral intake of electrolytes will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis, such as increased ventricular irritability.

Dilutional hyponatremia may occur in edematous patients; appropriate treatment is usually water restriction. In actual salt depletion, appropriate replacement is the treatment of choice. Chloride deficit is usually mild, not requiring specific treatment except in extraordinary circumstances (liver, renal disease). Thiazide-like diuretics have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Hyperurcemia may occur, and frank gout may be precipitated in certain patients receiving indapamide. Serum concentrations of uric acid should be monitored periodically.

Use with caution in patients with severe renal disease; consider withholding or discontinuing if progressive renal impairment is observed. Renal function tests should be performed periodically.

Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Lateral diabetes may become manifest and insulin requirements in diabetic patients may be altered during thiazide administration. A mean increase in glucose of 6.47 mg/dL was observed in patients treated with indapamide 1.25 mg, which was not considered clinically significant in these trials. Serum concentrations of glucose should be monitored routinely during treatment with indapamide.

Calcium excretion is decreased by diuretics pharmacologically related to indapamide. After six to eight weeks of indapamide 1.25 mg treatment and in long-term studies of hypertensive patients with higher doses of indapamide, however, serum concentrations of calcium increased only slightly with indapamide. Indapamide may decrease serum PBI levels without signs of thyroid disturbance. Complications of hyperparathyroidism have not been seen. Discontinue before tests of parathyroid function are performed.

Thiazides have exacerbated or activated systemic lupus erythematosus. Consider this possibility with indapamide.

DRUG INTERACTIONS: LOZOL may add to or potentiate the action of other antihypertensive drugs. The antihypertensive effect of the drug may be enhanced in the postsympathectomized patient. Indapamide may decrease arterial responsiveness to norepinephrine, but this does not preclude the use of norepinephrine.

In mouse and rat lifetime carcinogenicity studies, there were no significant differences in the incidence of tumors between the indapamide-treated animals and the control groups.

Pregnancy Category B: Diuretics cross the placental barrier and appear in cord blood. Indapamide should be used during pregnancy only if clearly needed. Use may be associated with fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse effects that have occurred in adults. It is not known whether this drug is excreted in human milk. If use of this drug is deemed essential, the patient should stop nursing.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. From Phase III placebo-controlled studies with indapamide 1.25 mg, adverse reactions with ≥5% cumulative incidence: headache, infection, pain, back pain, dizziness, rhinitis; <5% cumulative incidence: asthenia, flu syndrome, abdominal pain, chest pain, constipation, diarrhea, dyspepsia, nausea, peripheral edema, nervousness, hypertension, cough, pharyngitis, sinusitis, conjunctivitis. All other clinical adverse reactions occurred at an incidence of <1%. In controlled clinical trials of six to eight weeks in duration, 20% of patients receiving indapamide 1.25 mg, 61% of patients receiving indapamide 5.0 mg, and 80% of patients receiving indapamide 10.0 mg had at least one potassium value below 3.4 mEq/L. In the indapamide 1.25 mg group, about 40% of those patients who reported hypokalemia as a laboratory adverse event returned to normal serum potassium values without intervention. Hypokalemia with concomitant clinical signs or symptoms occurred in 2% of patients

receiving indapamide 1.25 mg. From Phase II placebo-controlled studies and long-term controlled clinical trials with LOZOL 2.5 mg or 5.0 mg, adverse reactions with ≥ 5% cumulative incidence: headache, dizziness, fatigue, weakness, loss of energy, lethargy, tiredness or malaise, muscle cramps or spasm or numbness of the extremities, nervousness, tension, anxiety, irritability or agitation; <5% cumulative incidence: lightheadedness, drowsiness, vertigo, insomnia, depression, blurred vision, constipation, nausea, vomiting, diarrhea, gastric irritation, abdominal pain or cramps, anorexia, orthostatic hypotension, premature ventricular contractions, irregular heart beat, palpitations, frequency of urination, nocturia, polyuria, rash, hives, pruritus, vasculitis, impotence or reduced libido, rhinorrhea, flushing, hyperurcemia, hyperglycemia, hyponatremia, hypochloremia, increase in serum BUN or creatinine, glycosuria, weight loss, dry mouth, tingling of extremities. Hypokalemia with concomitant clinical signs or symptoms occurred in 3% of patients receiving indapamide 2.5 mg q.d. and 7% of patients receiving indapamide 5 mg q.d. In long-term controlled clinical trials comparing the hypokalemic effects of daily doses of indapamide and hydrochlorothiazide, however, 47% of patients receiving indapamide 2.5 mg, 72% of patients receiving indapamide 5 mg, and 44% of patients receiving hydrochlorothiazide 50 mg had at least one potassium value (out of a total of 11 taken during the study) below 3.5 mEq/L. In the indapamide 2.5 mg group, over 50% of those patients returned to normal serum potassium values without intervention. Other adverse reactions reported with antihypertensive/diuretics are intrahepatic cholestatic jaundice, sialadenitis, xanthopsia, photosensitivity, purpura, bullous eruptions, Stevens-Johnson syndrome, necrotizing angitis, fever, respiratory distress (including pneumonitis), anaphylactic reactions, agranulocytosis, leukopenia, thrombocytopenia, aplastic anemia.

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription. Keep tightly closed. Store at controlled room temperature, 15°-30°C (59°-86°F). Avoid excessive heat. Dispense in light containers as defined in USP. See product circular for full prescribing information. Revised: 5/93

Reference: 1. Data on file, Rhône-Poulenc Rorer Pharmaceuticals Inc. Product of Servier Research Institute

rPr RHÔNE-POULENC RORER
RHÔNE-POULENC RORER PHARMACEUTICALS INC.
500 ARCO A ROAD
COLLEGEVILLE, PA 19306

©1994 Rhône-Poulenc Rorer Pharmaceuticals Inc.

FC#94-R52

Imagine
a long,
complex
form
required
to report
adverse
events.

Not
anymore.

1-800-FDA-1088.



If it's serious, we need to know.

ARCHIVES OF FAMILY MEDICINE

The ARCHIVES OF FAMILY MEDICINE is a member of the consortium of AMA journals listed below. The ARCHIVES reaches more than 81 500 readers in family and general practice each month, in addition to paid subscribers.

The Journal of the American Medical Association (JAMA)

Archives of Dermatology
Archives of Family Medicine
Archives of General Psychiatry
Archives of Internal Medicine
Archives of Neurology
Archives of Ophthalmology
Archives of Otolaryngology—Head & Neck Surgery
Archives of Pathology & Laboratory Medicine
Archives of Pediatrics & Adolescent Medicine
Archives of Surgery

The ARCHIVES OF FAMILY MEDICINE (ISSN 1063-3987) is published monthly by the American Medical Association, 515 N State St, Chicago, IL 60610, and is an official publication of the Association. Application to mail at second-class postage rates is paid at Chicago and at the additional mailing offices. GST registration number R126 225 556. Canada Post International Publications Mail (Canadian Distribution) Sales Agreement No. 319600. Printed in the USA.

SUBSCRIPTION RATES—The subscription rates for the ARCHIVES OF FAMILY MEDICINE are as follows: \$95 for 1 year, \$173 for 2 years in the United States and US possessions; other countries, one year, \$130; 2 years, \$243. (Rates for subscriptions for delivery to Japan or South Korea are available through exclusive agents—contact publisher.) Special rates for residents and medical students in the United States and US possessions are available. Address inquiries to Subscriber Services Center, American Medical Association, PO Box 10945, Chicago, IL 60610. Phone (800) 262-2350. Fax: (312) 464-5831. For mailing addresses outside the US and US possessions, see International Subscription Information.

CHANGE OF ADDRESS—POSTMASTER, send all address changes to Subscriber Services, American Medical Association, 515 N State St, Chicago, IL 60610. Please notify us of address change at least 6 weeks in advance to ensure uninterrupted service. Include both old and new addresses, a recent mailing label, and new ZIP code. For mailing addresses outside the US and US possessions, see International Subscription Information.

SUBSCRIBER SERVICES—For information about subscribing to any of the AMA publications, change of address, missing issues, or purchasing back issues, please contact Subscriber Services, American Medical Association, PO Box 10945, Chicago, IL 60610, or call (800) 262-2350 (670-7827) between 8:30 AM and 4:30 PM CST. Fax: (312) 464-5831. For mailing addresses outside the US and US possessions, see International Subscription Information.

INTERNATIONAL SUBSCRIPTION INFORMATION—Subscriptions outside the United States and US possessions are served according to geographic region. Please address correspondence to the following offices: For subscription delivery in North America, Central America, and South America, contact Subscriber Services Center, PO Box 10945, Chicago, IL 60610, USA. Tel: 1-312-760-7827, Fax: 1-312-464-5831. For subscription delivery in all other areas, contact: JAMA & Archives Journals Reader Services Centre, PO Box 299, London, England WC1H 9TD. Tel: 44-(0)71-383 6270, Fax: 44-(0)71-383 6402.

REPRINTS—Authors place their reprint order at the time the edited typescript is reviewed and should allow 4 to 6 weeks for delivery following publication. Requests for individual reprints should be sent directly to the author at the address shown in the article.

For bulk reprint orders for commercial distribution please contact Mark Kuhns, 600 Third Ave, New York, NY 10016, phone (212) 867-6640, fax (212) 953-2497. For reprint orders in limited quantities for educational distribution please contact Rita Houston, 515 N State St, Chicago, IL 60610, phone (312) 464-2512, fax (312) 464-5835.

PERMISSIONS—Contact Laslo Hunyady, Permissions Assistant, 515 N State St, Chicago, IL 60610, phone (312) 464-2513.

ADVERTISING PRINCIPLES—Each advertisement in this issue has been reviewed and complies with the principles governing advertising in AMA scientific publications. A copy of these principles is available on request. The appearance of advertising in AMA publications is not an AMA guarantee or endorsement of the product or the claims made for the product by the manufacturer.

ARCHIVES

OF

FAMILY MEDICINE

VOL 3 NO. 7, JULY 1994

Living in Medicine

- When Your Mother Is a Doctor:
For Dawna LaVina, MD** 570
LaVina Jean Armstrong

Letters to the Editor

- Recognition of and Referral
for Domestic Violence** 573
David H. Thom, MD, PhD

- Empiric Antibiotics in Sinusitis** 573
Anthony J. Geraci, Jr, MD

- The Question of Clarithromycin:
A First-Line Drug for Sinusitis?** 574
*Robert W. Tahara, MD; Steve Oosterman, DO;
W. R. Kiser, MD, MA*

- Multicenter Comparison
of Clarithromycin and Amoxicillin** 574
George S. Rust, MD, MPH

- In Reply** 575
Karen H. Calhoun, MD

Editorials

- Computer-Assisted Preventive Care:
Time to 'Byte' the Bullet?** 576
Stephen J. McPhee, MD

- Preventive Medicine for Adolescents:
A Hopeless Cause or a Research
Challenge for Family Physicians** 579
Walter W. Rosser, MD

Original Contributions

- Computer-Based vs Manual Health
Maintenance Tracking: A Controlled Trial** 581
*Paul S. Frame, MD; James G. Zimmer, MD;
Paula L. Werth, MPS; W. Jackson Hall, PhD;
Shirley W. Eberly, MS*

- Antiepileptics in the Elderly:
Pharmacoepidemiology
and Pharmacokinetics** 589
*James C. Cloyd, PharmD;
Thomas E. Lackner, PharmD;
Ilo E. Leppik, MD*

American Medical Association

Physicians dedicated to the health of America



Copyright 1994 by the American Medical Association. All rights reserved.
Reproduction without permission is prohibited.

All articles published, including editorials, letters, and book reviews, represent the opinions of the authors and do not reflect the policy of the American Medical Association, the Editorial Board, or the institution with which the author is affiliated, unless this is clearly specified.

James S. Todd, MD
Executive Vice President
Kenneth E. Monroe
Deputy Executive Vice President
Larry E. Joyce
Senior Vice President
George D. Lundberg, MD
Editor-in-Chief, Scientific
Publications
Robert L. Kennett
Vice President, Publishing
Nawin Gupta, PhD
Director, Publishing Operations
Division
Cheryl Iverson
Director, Editorial Processing
Division

Michael D. Springer
Associate Publisher
John P. Cahill
Manager, Advertising Sales
Geoffrey A. Flick
Manager, Marketing Services

Advertising Offices: East: Phillip B. Altamore, Donald M. Blatherwick, John L. Reeves, 600 Third Ave, Suite 3700, New York, NY 10016 (212) 867-6640. **Diagnostics/Devices:** M. J. Mrvica Associates, 155 S White Horse Pike, Berlin, NJ 08009; (609) 768-9360. **Midwest/Far West:** Peter L. Payerli, 515 N State St, Chicago, IL 60610 (312) 464-2429.



RELAFEN[®]
NABUMETONE



SmithKline Beecham
Pharmaceuticals

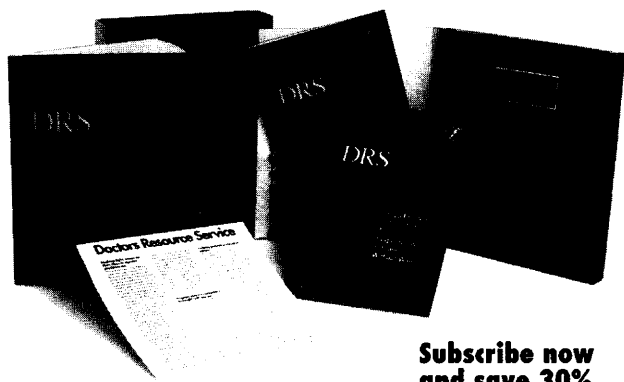
©SmithKline Beecham, 1993
Philadelphia, PA 19101

The last word in managed care is still care!

If you think there's too much management and not enough care in managed care, remember this. The last word in health has always been care. And the front line will always be doctors.

Doctors Resource Service

DRS, which is AMA's managed care/health system reform resource series, puts it all into perspective. How to balance management with care. How to respond to reform. How to protect your personal and professional future.



**Subscribe now
and save 30%**

DRS puts the balance in managed care. Specific topics include:
• Competition • PHOs • Financing MD corporations • Negotiating contracts • Anti-trust • Evaluating compensation • Selling, merging, buying • Assets • Capital development • Quality assessment
• Regulations • Legal rights • Gatekeepers • Managing your personal and professional life • Trade-offs and risks in employment

New *DRS* subscribers save 30%! Subscribe now and get the first two issues of *DRS* for only \$30. In addition, take 30% off the next seven issues. Special reduced subscription rate is \$210 for AMA members and \$338 for nonmembers (applicable state sales tax and shipping and handling will be added).

Use the following order numbers for this special discount offer:

DRS, Issues 1 and 2 Order #: OP636094MH

DRS subscription, Issues 3-9 Order #: OP636194MH

Call today and have the last word in managed care!

800 621-8335

Visa, MasterCard, American Express/Optima accepted

American Medical Association

Physicians dedicated to the health of America



ARCHIVES OF FAMILY MEDICINE

Publication Staff
Offices: 515 N State St
Chicago, IL 60610

Editorial Processing Department,
Specialty Journals

Director: Paula Glitman
Manager: Barbara Clark
Freelance Manager:
Vickey Golden
Assistant Freelance Coordinator:
Richard T. Porter
Senior Copy Editor/Atex Specialist:
Paul Frank
Senior Copy Editor:
Janice Snider
Copy Editors:
Diane L. Cannon
Gwen Chaffen
Mary E. Coerver
Vonda L. Meltesen
Manuscript Records Clerk:
Tonja Glover

Production & Distribution
Department

Director: Carl Braun
Manager: Carole Piszker
Production Associates:
Debbie Pogorzelski
Christine M. Wagenknecht
E. Ruth White
Senior Production Assistant:
Kira Culver
Production Assistant:
Jo Anne Turner
Manager, Distribution:
Paul Gasielki

Publishing Operations Division
Office

Manager, Budgets & Costs:
Bonnie Van Clevon
Manager, Advertising Production:
Vanessa Hayden
Staff Assistant: Diane Darnell
Office Manager: Karen Branham
Production Assistant:
Valerie Balkcom

Electronic Publishing Department

Director: Mary C. Steermann
Assistant Director: Jaye Matthews
Manager, Color:
Thomas J. Handrigan
Graphics & Color Coordinator:
JoAnne Weiskopf
Electronic Coordinator:
Mary Ellen Johnston
Graphic Designer:
Charl Richey-Davis
Electronic Production Associate:
Linda Knott
Electronic Production Operators:
Gail Barrett
Brenda Chandler-Haynes
Michael L. Culbert
Leslie Koch
Mary Ann Kuranda
Sandra Lopez
Peter Watkins
Alicja Wojcik
Graphics Operators:
Carolyn Luton
Regina Vander Reyden
Manager, Proofreading:
Teresa H. Omiotek

Proofreaders:
David Antos
Brenda J. Gregoline
Daniel James

Production Assistant: Janey Stennis

Circulation Department

Director: Beverly Martin
Reprints: Rita Houston

Specialty Journal Division Office

Administrative Assistant:
Marla Hall

Licensing & Indexing Department

Director: Norman Frankel
Staff:
George Kruto
Mary Kay Tinerella
Permissions: Laslo Hunyady



ONCE-A-DAY

CARDIZEM[®] CD

(diltiazem HCl) 120-, 180-, 240-, 300-mg Capsules

**IN HYPERTENSION
OR ANGINA**



CVM94021201

1122C4

IN HYPERTENSION OR ANGINA

CARDIZEM[®] CD

(diltiazem HCl)

**FOR EFFECTIVE
24-HOUR CONTROL**



ONCE A DAY

HEMODYNAMIC EFFECTS

In hypertension¹

- The magnitude of blood pressure reduction is related to the degree of hypertension
- Low incidence of vasodilatory side effects
- No reflex tachycardia is associated with chronic antihypertensive effects

In angina¹

- Potent dilator of coronary arteries* and reduces vasospasm
- Appropriate decrease in heart rate with a low incidence (<1%) of reflex tachycardia
- Little or no negative inotropic effect in patients with normal ventricular function[†]

WELL-TOLERATED CONTROL REGARDLESS OF AGE OR GENDER[‡]

- A side-effect discontinuation rate comparable to placebo in both hypertension and angina trials²
- 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%)¹

* Demonstrated in patients with vasospastic angina.

† See Warnings and Clinical Pharmacology sections in prescribing information.

‡ In clinical trials with Cardizem CD.

Please see brief summary of prescribing information on next page.



ONCE - A - DAY

CARDIZEM[®] CD

(diltiazem HCl) 120-, 180-, 240-, 300-mg Capsules

FOR HYPERTENSION OR ANGINA



ONCE - A - DAY CARDIZEM® CD

(diltiazem HCl) 120-, 180-, 240-, 300-mg Capsules

Rx
Cardizem CD
Start with one
180-mg
capsule daily

FOR HYPERTENSION OR ANGINA

Brief Summary of
Prescribing Information as of April 1993

CARDIZEM® CD (diltiazem HCl) Capsules

CONTRAINDICATIONS

CARDIZEM 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 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

- Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3290 patients or 0.40%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
- Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of CARDIZEM (diltiazem hydrochloride) in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.
- Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
- Acute Hepatic Injury.** Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General

CARDIZEM (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 drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological 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.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions

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

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM 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, dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, may require adjustment when starting or stopping concomitantly administered diltiazem to maintain optimum therapeutic blood levels.

Beta-blockers. Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. In vitro, propranolol appears to be displaced from its binding sites by diltiazem. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine. A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1200 mg per day and a single dose of diltiazem 60 mg. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis. Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics. The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Cyclosporine. A pharmacokinetic interaction between diltiazem and cyclosporine has been observed during studies involving renal and cardiac transplant patients. In renal and cardiac transplant recipients, a reduction of cyclosporine dose ranging from 15% to 48% was necessary to maintain cyclosporine trough concentrations similar to those seen prior to the addition of diltiazem. If these agents are to be administered concurrently, cyclosporine concentrations should be monitored, especially when diltiazem therapy is initiated, adjusted, or discontinued. The effect of cyclosporine on diltiazem plasma concentrations has not been evaluated.

Carbamazepine. Concomitant administration of diltiazem with carbamazepine has been reported to result in elevated serum levels of carbamazepine (40% to 72% increase), resulting in toxicity in some cases. Patients receiving these drugs concurrently should be monitored for a potential drug interaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy

Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare 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 up to 360 mg with rates in placebo patients shown for comparison.

CARDIZEM CD Capsule Placebo-Controlled Angina and Hypertension Trials Combined		
Adverse Reactions	Cardizem CD (n=607)	Placebo (n=301)
Headache	5.4%	5.0%
Dizziness	3.0%	3.0%
Bradycardia	3.3%	1.3%
AV Block First Degree	3.3%	0.0%
Edema	2.6%	1.3%
ECG Abnormality	1.6%	2.3%
Asthenia	1.8%	1.7%

In clinical trials of CARDIZEM CD capsules, CARDIZEM tablets, and CARDIZEM SR capsules involving over 3200 patients, the most common events (ie, greater than 1%) were edema (4.6%), headache (4.6%), dizziness (3.5%), asthenia (2.6%), 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

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor

Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeusia, dyspepsia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hepatic warnings), thirst, vomiting, weight increase

Dermatological: Petechiae, photosensitivity, pruritus, urticaria

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarthral pain, polyuria, sexual difficulties

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, erythema multiforme, exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well-documented cases of generalized rash, characterized as leukocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and CARDIZEM therapy is yet to be established.

Prescribing Information as of April 1993

Marion Merrell Dow Inc.
Kansas City, MO 64114

ccdb0493a

References: 1. Cardizem CD prescribing information. 2. Data on file, Marion Merrell Dow Inc.



MARION MERRELL DOW INC.
U S A
KANSAS CITY, MO 64114

Information to share

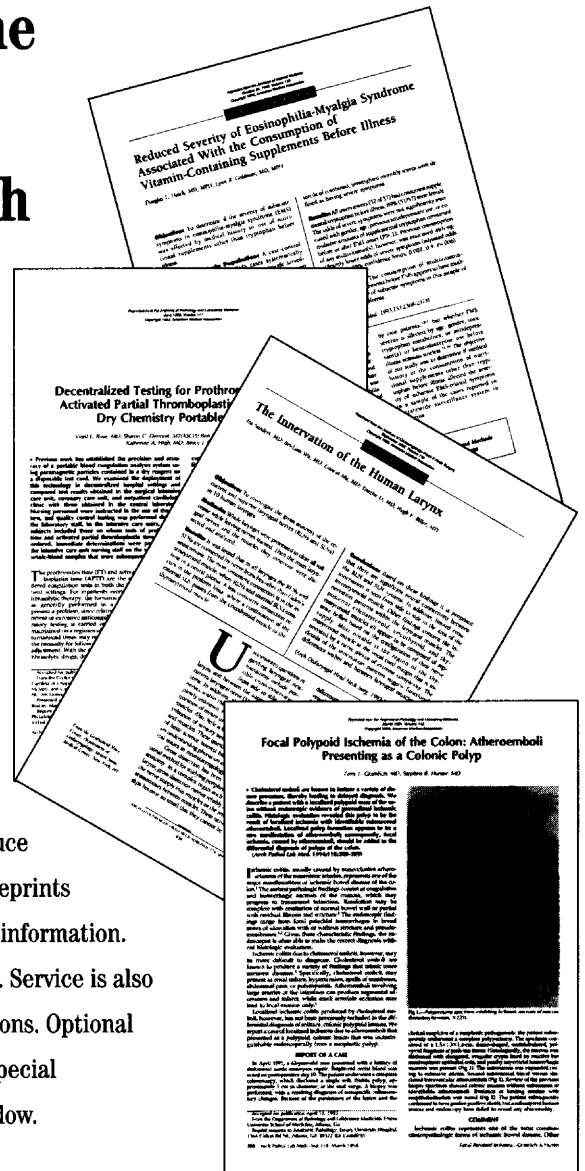
Authorized reprints are the convenient way to provide students or colleagues with important articles.

We take care of all the work

When you have an educational use for an original article from JAMA: The Journal of the American Medical Association or the Archives journals, save the time and effort of obtaining permissions, organizing and copying. Just place an order to purchase authorized reprints of original articles. Reprints will be delivered ready for distribution in the classroom, at seminars and conferences, or to your colleagues in medicine.

Quality, fully-authorized reprints

Printed in black ink on glossy, high-quality paper, reprints reproduce the original article as it first appeared in JAMA or the Archives. Reprints measure 8 x 10 3/4 inches (205 x 275 mm), and include full credit information. Reprints are available for purchase in any quantity of 300 or more. Service is also available for articles with color photographs, charts, and illustrations. Optional features include 3-hole punches and shrink-wrapping. For other special requirements, contact the Reprints Coordinator at the address below.



JAMA: The Journal of the American Medical Association • Archives of Dermatology • Archives of Family Medicine • Archives of General Psychiatry
Archives of Internal Medicine • Archives of Neurology • Archives of Ophthalmology • Archives of Otolaryngology-Head & Neck Surgery
Archives of Pathology & Laboratory Medicine • Archives of Pediatrics & Adolescent Medicine • Archives of Surgery

For more information...

Please send me information on purchasing authorized educational reprints in bulk for articles published in JAMA: The Journal of the American Medical Association and the Archives journals.

Name _____
Company or Organization _____
Address _____
City & Postal Code _____ Country _____
FAX _____

Mail to: Reprints Coordinator
515 North State Street
Chicago, IL 60610 USA
Tel: 1-312-464-2521 FAX: 1-312-464-5831

American Medical Association
Physicians dedicated to the health of America



Stress: The Profession, the Family and You

International Conference on Physician Health

September 16-20, 1994

Ottawa Westin Hotel

Ottawa, Ontario, Canada

Sponsored by the American Medical Association,
the Canadian Medical Association,
the Federation of State Medical Boards, and
the Federation of Medical Licensing Authorities of Canada.

Health related problems are on our minds and in our news, affecting the way we live, the way we interact, the way we plan for our futures. They contribute to the amount of stress we face during the course of a normal day.

Physicians are often ill-prepared to recognize stress-related problems in themselves, their families or their colleagues.

Now you can discover more about how your colleagues are facing their own health challenges – at a meeting on physicians' health related concerns, the *International Conference on Physician Health*.

The Conference provides an opportunity to hear about the latest research findings on physician health, as well as new and innovative treatment and education programs in the area.

Key Note Speakers will include:

Roy W. Menninger, MD, Chairman of Trustees, Menninger Foundation speaking on the general conference theme from the US perspective, and

Michael F. Myers, MD, Department of Psychiatry, University of British Columbia speaking on the general conference theme from the Canadian perspective

Other Speakers will include:

Erica Frank, MD, on the Women Physicians Health Study

Joseph Newman, MD, on Disability due to Illness

James Winn, MD, on Physician Health and Medical Licensing Boards

While you explore the issues, take advantage of the Ottawa Westin Hotel's location for a personal health break. Ottawa is Canada's capital and offers many national museums, over 60 miles of bicycle paths, and hiking in Gatineau Park and along the Rideau Canal.

For additional information on how to register for this important Conference, write or call: International Conference on Physician Health, American Medical Association, 515 N. State Street, Chicago, IL. 60610. Telephone: 800 621-8335.

American Medical Association

Physicians Health Foundation

Caring for the Caregiver



Calan® SR (verapamil hydrochloride)

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see Warnings), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in an increased sensitivity to lithium (neurotoxicity), with either no change or an increase in serum lithium levels; however, it may also result in a lowering of serum lithium levels. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. There was no evidence of a carcinogenic potential of verapamil administered to rats for 2 years. A study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia, HR < 50/min (1.4%), AV block, total 1°, 2°, 3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

2/13/92 • P91CA7196V

Address medical inquiries to:
G.D. Searle & Co.
Medical & Scientific
Information Department
4901 Searle Parkway
Skokie, IL 60077

SEARLE

Box 5110
Chicago, IL 60680-5110

C94CA9530T

*For the Management of
Mild to Moderate Hypertension*



ONCE-DAILY
Calan[®] SR
(verapamil HCl)
SUSTAINED-RELEASE CAPLETS



Excellence Built On Basics

The recommended starting dosage for Calan SR is 180 mg once daily. Dose titration will be required in some patients to achieve blood pressure control. A lower starting dosage of 120 mg/day may be warranted in some patients (eg, the elderly, patients of small stature). Dosages above 240 mg daily should be administered in divided doses. Calan SR should be administered with food. Constipation, which is easily managed in most patients, is the most commonly reported side effect of Calan SR. Verapamil should be administered cautiously to patients with impaired renal function.

Please see following page for brief summary of complete prescribing information.

©1994 Searle

SEARLE