

INTRODUCING DIFLUCAN® (FLUCONAZOLE) 150 MG

"Just one pill,
it was so easy."

"I like that
you can take
it anytime."

"I didn't have to deal
with any of the mess."

"I felt better
the first day,
and great
the second."

† Two open-label, multicenter, randomized trials comparing a single oral Diflucan tablet (150 mg) with either 2% miconazole cream (100 mg) once nightly for 7 days or clotrimazole vaginal tablets (100 mg) once nightly for 7 days in 870 women with vaginal yeast infection due to *Candida*. Clinical cure: complete resolution of signs and symptoms present at the initial assessment; mycologic cure: negative results from both vaginal fungal culture and KOH preparation.

‡ Results of two open, multicenter studies of single-dose Diflucan (150 mg) in 188 and 180 women, respectively, with vaginal yeast infections. Patients responding to treatment were asked to estimate times from start of therapy to onset of relief and to complete relief.

§ Wholesale acquisition cost (WAC) provided by *Medi-Span*®, July 1994. WAC may not necessarily reflect actual pharmacy or out-of-pocket costs. In studies of Diflucan, the clinical and mycologic cure rates in the fluconazole group were comparable with those of the vaginal product group (clotrimazole and miconazole). WAC includes Gyne-Lotrimin® (a registered trademark of Schering-Plough Corp); and Terazol® and Monistat® 7 (both registered trademarks of Ortho Pharmaceutical Corp).

Please see brief summary of prescribing information on last page of this advertisement.

THE ONLY ORAL ONE-DOSE CURE FOR MOST VAGINAL YEAST* INFECTIONS

GREAT NEWS FOR WOMEN IS HERE

Clinical and mycologic cure comparable with 7-day topicals in two separate trials—

One oral Diflucan 150-mg tablet has been shown to be as effective as 7 nights of 2% miconazole cream (100 mg) or 7 nights of clotrimazole vaginal tablets (100 mg).^{1†}

Early symptom relief—In two additional studies of 368 women taking Diflucan, median time to start of symptom relief was 1 day (range: 0.04 to 10 days) and 2 days (range: 0.5 to 20 days) to complete relief.^{1-3‡}

Patients may require reevaluation should symptoms not improve within 3 to 5 days.

Established safety experience—More than 9 million patient days of therapy at the 150-mg dose worldwide. In US clinical trials with 870 women, the most common side effects with Diflucan were headache (13%), nausea (7%), and abdominal pain (6%).¹

Patients respond to one-dose oral convenience

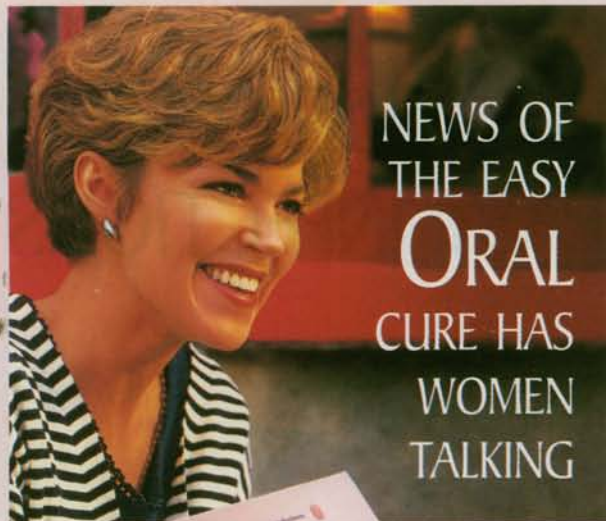
Easy to take—Diflucan can be taken anytime, anywhere, day or night, with or without food.¹

Less expensive—Diflucan provides full-course therapy that costs less than leading prescription and most OTC products.^{1§}

*Due to *Candida*

NEW INDICATION
Diflucan[®]
(fluconazole 150-mg tablet)

THE EASY ORAL CURE



NEWS OF THE EASY ORAL CURE HAS WOMEN TALKING



DOSING:
A single 150-mg
Oral tablet for most
vaginal yeast* infections

NEW INDICATION
Diflucan[®]
(fluconazole 150-mg tablet)

*Due to *Candida*

Please see brief summary of prescribing information on this page.

References: 1. Data on file. Pfizer Inc. 2. A comparison of single-dose oral fluconazole with 3-day intravaginal clotrimazole in the treatment of vaginal candidiasis: report of an international multicentre trial. *Br J Obstet Gynecol.* 1989;96:226-232. 3. Treatment of vaginal candidiasis with a single oral dose of fluconazole. *Eur J Clin Microbiol Infect Dis.* 1988;7:364-367.

DIFLUCAN BRIEF SUMMARY FOR VAGINAL CANDIDIASIS

INDICATION

DIFLUCAN[®] (fluconazole 150-mg oral tablet) is indicated for the treatment of vaginal candidiasis (vaginal yeast infections due to *Candida*).

CONTRAINDICATIONS

DIFLUCAN (fluconazole) is contraindicated in patients who have shown hypersensitivity to fluconazole or to any of its excipients. There is no information regarding cross hypersensitivity between fluconazole and other azole antifungal agents. Caution should be used in prescribing DIFLUCAN to patients with hypersensitivity to other azoles.

WARNINGS

(1) **Hepatic injury:** DIFLUCAN has been associated with rare cases of serious hepatic toxicity, including fatalities primarily in patients with serious underlying medical conditions. In cases of DIFLUCAN associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of the patient has been observed. Patients who develop abnormal liver function tests during DIFLUCAN therapy should be monitored for the development of more severe hepatic injury.

(2) **Anaphylaxis:** In rare cases, anaphylaxis has been reported.

(3) **Dermatologic:** Patients have rarely developed exfoliative skin disorders during treatment with DIFLUCAN. Patients who develop rashes during treatment with DIFLUCAN should be monitored closely.

PRECAUTIONS

The convenience and efficacy of the single-dose oral tablet of fluconazole regimen for the treatment of vaginal yeast infections should be weighed against the acceptability of a higher incidence of drug related adverse events with DIFLUCAN (26%) versus topical agents (16%) in U.S. comparative clinical studies (See Adverse Reactions.)

Drug Interactions

Clinically significant hypoglycemia may be precipitated by the use of DIFLUCAN with oral hypoglycemic agents; one fatality has been reported from hypoglycemia in association with combined DIFLUCAN and glyburide use. DIFLUCAN reduces the metabolism of tolbutamide, glyburide, and glipizide and increases the plasma concentration of these agents. When DIFLUCAN is used concomitantly with these or other sulfonylurea oral hypoglycemic agents, blood glucose concentrations should be carefully monitored and the dose of the sulfonylurea should be adjusted as necessary.

Prothrombin time may be increased in patients receiving concomitant DIFLUCAN and coumarin-type anticoagulants. Careful monitoring of prothrombin time in patients receiving DIFLUCAN and coumarin-type anticoagulants is recommended.

DIFLUCAN increases the plasma concentrations of phenytoin. Careful monitoring of phenytoin concentrations in patients receiving DIFLUCAN and phenytoin is recommended.

DIFLUCAN may significantly increase cyclosporine levels in renal transplant patients with or without renal impairment. Careful monitoring of cyclosporine concentrations and serum creatinine is recommended in patients receiving DIFLUCAN and cyclosporine.

Rifampin enhances the metabolism of concurrently administered DIFLUCAN. Depending on clinical circumstances, consideration should be given to increasing the dose of DIFLUCAN when it is administered with rifampin.

DIFLUCAN increased the serum concentrations of theophylline. Careful monitoring of serum theophylline concentrations in patients receiving DIFLUCAN and theophylline is recommended.

Because of the occurrence of serious cardiac dysrhythmias in patients receiving other azole antifungals in conjunction with terfenadine, an interaction study has been performed, and failed to demonstrate a clinically significant drug interaction. Although these events have not been observed in patients receiving DIFLUCAN, the co-administration of DIFLUCAN and terfenadine should be carefully monitored.

Fluconazole tablets coadministered with ethinyl estradiol- and levonorgestrel-containing oral contraceptives produced an overall mean increase in ethinyl estradiol and levonorgestrel levels; however, in some patients there were decreases up to 47% and 33% of ethinyl estradiol and levonorgestrel levels. The data presently available indicate that the decreases in some individual ethinyl estradiol and levonorgestrel AUC values with fluconazole treatment are likely the result of random variation. While there is evidence that fluconazole can inhibit the metabolism of ethinyl estradiol and levonorgestrel, there is no evidence that fluconazole is a net inducer of ethinyl estradiol or levonorgestrel metabolism. The clinical significance of these effects is presently unknown.

Physicians should be aware that interaction studies with medications other than those listed in the Clinical Pharmacology section have not been conducted, but such interactions may occur.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Fluconazole showed no evidence of carcinogenic potential in mice and rats treated orally for 24 months at doses of 2.5, 5 or 10 mg/kg/day (approximately 2-7x the recommended human dose). Male rats treated with 5 and 10 mg/kg/day had an increased incidence of hepatocellular adenomas.

Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in 4 strains of *S. typhimurium*, and in the mouse lymphoma L5178Y system. Cytogenetic studies *in vivo* (murine bone marrow cells, following oral administration of fluconazole) and *in vitro* (human lymphocytes exposed to fluconazole at 1000 µg/mL) showed no evidence of chromosomal mutations.

Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10 or 20 mg/kg or with parenteral doses of 5, 25 or 75 mg/kg, although the onset of parturition was slightly delayed at 20 mg/kg p.o. In an intravenous perinatal study in rats at 5, 20 and 40 mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg (approximately 5-15x the recommended human dose) and 40 mg/kg, but not at 5 mg/kg. The disturbances in parturition were reflected by a slight increase in the number of still-born pups and decrease of neonatal survival at these dose levels. The effects on parturition in rats are consistent with the species specific estrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole.

Pregnancy

Teratogenic Effects. Pregnancy Category C: Fluconazole was administered orally to pregnant rabbits during organogenesis in two studies, at 5, 10 and 20 mg/kg, and at 5, 25, and 75 mg/kg respectively. Maternal weight gain was impaired at all dose levels, and abortions occurred at 75 mg/kg (approximately 20-60x the recommended human dose); no adverse fetal effects were detected. In several studies in which pregnant rats were treated orally with fluconazole during organogenesis, maternal weight gain was impaired and placental weights were increased at 25 mg/kg. There were no fetal effects at 5 or 10 mg/kg; increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg (approximately 20-60x the recommended human dose) to 320 mg/kg embryoletality in rats was increased and fetal abnormalities included wavy ribs, cleft palate and abnormal cranio-facial ossification. These effects are consistent with the inhibition of estrogen synthesis in rats and may be a result of known effects of lowered estrogen on pregnancy, organogenesis and parturition.

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

Nursing Mothers

Fluconazole is secreted in human milk at concentrations similar to plasma. Therefore, the use of DIFLUCAN in nursing mothers is not recommended.

Pediatric Use

Efficacy of DIFLUCAN has not been established in children. A small number of patients from age 3 to 13 years have been treated safely with DIFLUCAN using doses of 3-6 mg/kg daily.

The safety and effectiveness of DIFLUCAN 150 mg tablets in the treatment of vaginal candidiasis in patients under 18 years of age have not been established.

ADVERSE REACTIONS

In patients receiving a single dose for vaginal candidiasis.

During comparative clinical studies conducted in the United States, 448 patients with vaginal candidiasis were treated with DIFLUCAN, 150 mg single dose. The overall incidence of side effects possibly related to DIFLUCAN was 26%. In 422 patients receiving active comparative agents, the incidence was 16%. The most common treatment-related adverse events reported in the patients who received 150 mg single dose fluconazole for vaginitis were headache (13%), nausea (7%) and abdominal pain (6%). Other side effects reported with an incidence equal to or greater than 1% included diarrhea (3%), dyspepsia (1%), dizziness (1%), and taste perversion (1%). Most of the reported side effects were mild to moderate in severity. Rarely, angioedema and anaphylactic reaction have been reported in marketing experience.

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 complete text of all AMA journals is available on the MEDIS database from Mead Data Central, Dayton, Ohio.

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. Second-class postage rates paid at Chicago and at additional mailing office. 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 the 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 Archives of Family Medicine, c/o 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 Center, American Medical Association, PO Box 10945, Chicago, IL 60610, or call (312) 670-SUBS (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, American Medical Association, 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.

DDAVP® Nasal Spray

(desmopressin acetate) 5mL

BRIEF SUMMARY

CONTRAINDICATION: Known hypersensitivity to DDAVP Nasal Spray.

WARNINGS:

1. For intranasal use only.
2. In very young and elderly patients in particular, fluid intake should be adjusted downward in order to decrease the potential occurrence of water intoxication and hyponatremia. Particular attention should be paid to the possibility of the rare occurrence of an extreme decrease in plasma osmolality that may result in seizures which could lead to coma.

PRECAUTIONS:

General: DDAVP Nasal Spray at high dosage has infrequently produced a slight elevation of blood pressure, which disappeared with a reduction in dosage. The drug should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease because of possible rise in blood pressure.

DDAVP Nasal Spray should be used with caution in patients with conditions associated with fluid and electrolyte imbalance, such as cystic fibrosis, because these patients are prone to hyponatremia.

Rare severe allergic reactions have been reported with DDAVP. Anaphylaxis has been reported with intravenous administration of DDAVP Injection, but not with DDAVP intranasal.

Central Cranial Diabetes Insipidus: Since DDAVP Nasal Spray is used intranasally, changes in the nasal mucosa such as scarring, edema, or other disease may cause erratic, unreliable absorption in which case DDAVP Nasal Spray should not be used. For such situations, DDAVP Injection should be considered.

Primary Nocturnal Enuresis: If changes in the nasal mucosa have occurred, unreliable absorption may result. DDAVP Nasal Spray should be discontinued until the nasal problems resolve.

Information for Patients: Patients should be informed that the bottle accurately delivers 50 doses of 10 mcg each. Any solution remaining after 50 doses should be discarded since the amount delivered thereafter may be substantially less than 10 mcg of drug. No attempt should be made to transfer remaining solution to another bottle. Patients should be instructed to read accompanying directions on use of the spray pump carefully before use.

Laboratory Tests: Laboratory tests for following the patient with central cranial diabetes insipidus or post-surgical or head trauma-related polyuria and polydipsia include urine volume and osmolality. In some cases plasma osmolality may be required. For the healthy patient with primary nocturnal enuresis, serum electrolytes should be checked at least once if therapy is continued beyond 7 days.

Drug Interactions: Although the pressor activity of DDAVP Nasal Spray is very low compared to the antidiuretic activity, use of large doses of DDAVP Nasal Spray with other pressor agents should only be done with careful patient monitoring.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Teratology studies in rats have shown no abnormalities. No further information is available.

Pregnancy-Category B: Reproduction studies performed in rats and rabbits with doses up to 12.5 times the human intranasal dose (i.e., about 125 times the total adult human dose given systemically) have revealed no evidence of harm to the fetus due to desmopressin acetate. There are several publications of management of diabetes insipidus in pregnant women with no harm to the fetus reported; however, no controlled studies in pregnant women have been carried out. Published reports stress that, as opposed to preparations containing the natural hormones, DDAVP Nasal Spray (desmopressin acetate) in antidiuretic doses has no uterotropic action, but the physician will have to weigh possible therapeutic advantages against possible dangers in each individual case.

Nursing Mothers: There have been no controlled studies in nursing mothers. A single study in a post-partum woman demonstrated a marked change in plasma, but little if any change in assayable DDAVP Nasal Spray in breast milk following an intranasal dose of 10 mcg.

Pediatric Use: Primary Nocturnal Enuresis: DDAVP Nasal Spray has been used in childhood nocturnal enuresis. Short-term (4-8 weeks) DDAVP Nasal Spray administration has been shown to be safe and modestly effective in children aged 6 years or older with severe childhood nocturnal enuresis. Adequately controlled studies with DDAVP Nasal Spray in primary nocturnal enuresis have not been conducted beyond 4-8 weeks. The dose should be individually adjusted to achieve the best results.

Central Cranial Diabetes Insipidus: DDAVP Nasal Spray has been used in children with diabetes insipidus. Use in infants and children will require careful fluid intake restriction to prevent possible hyponatremia and water intoxication. The dose must be individually adjusted to the patient with attention in the very young to the danger of an extreme decrease in plasma osmolality with resulting convulsions. Dose should start at 0.05 mL or less.

Since the spray cannot deliver less than 0.1 mL (10 mcg), smaller doses should be administered using the rhinal tube delivery system. Do not use the nasal spray in pediatric patients requiring less than 0.1 mL (10 mcg) per dose. There are reports of an occasional change in response with time, usually greater than 6 months. Some patients may show a decreased responsiveness, others a shortened duration of effect. There is no evidence this effect is due to the development of binding antibodies but may be due to a local inactivation of the peptide.

ADVERSE REACTIONS: Infrequently, high dosages have produced transient headache and nausea. Nasal congestion, rhinitis and flushing have also been reported occasionally along with mild abdominal cramps. These symptoms disappeared with reduction in dosage. Nosebleed, sore throat, cough and upper respiratory infections have also been reported.

The following table lists the percent of patients having adverse experiences without regard to relationship to study drug from the pooled pivotal study data for nocturnal enuresis.

	PLACEBO (N=59) %	DDAVP 20 mcg (N=60) %	DDAVP 40 mcg (N=61) %
ADVERSE REACTION			
BODY AS A WHOLE			
Abdominal Pain	0	2	2
Asthenia	0	0	2
Chills	0	0	2
Headache	0	2	5
Throat Pain	2	0	0
NERVOUS SYSTEM			
Depression	2	0	0
Dizziness	0	0	3
RESPIRATORY SYSTEM			
Epistaxis	2	3	0
Nasal Pain	0	2	0
Respiratory Infection	2	0	0
Rhinitis	2	8	3
CARDIOVASCULAR SYSTEM			
Vasodilation	2	0	0
DIGESTIVE SYSTEM			
Gastrointestinal Disorder	0	2	0
Nausea	0	0	2
SKIN & APPENDAGES			
Leg Rash	2	0	0
Rash	2	0	0
SPECIAL SENSES			
Conjunctivitis	0	2	0*
Edema Eyes	0	2	0
Lachrymation Disorder	0	0	2

OVERDOSAGE: See adverse reactions above. In case of overdosage, the dose should be reduced, frequency of administration decreased, or the drug withdrawn according to the severity of the condition. There is no known specific antidote for DDAVP Nasal Spray.

An oral LD₅₀ has not been established. An intravenous dose of 2 mg/kg in mice demonstrated no effect.

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.

Please see product circular for full prescribing information.

REFERENCES: 1. Rittig S, Knudsen UB, Sørensen S: Long-term double-blind cross-over study of desmopressin intranasal spray in the management of nocturnal enuresis. In Meadow SR, ed. *Desmopressin in Nocturnal Enuresis: Proceedings of an international symposium*. England: Horus Medical Publications; 1988:43-54. 2. Miller K, Klauber GT: Desmopressin acetate in children with severe primary nocturnal enuresis. *Clin Ther* 1990;12(4):357-366. 3. Aladjem M, Wohl R, Boichis H, et al: Desmopressin in nocturnal enuresis. *Arch Dis Child* 1982;57:137-140. 4. Bloom DA: The American experience with desmopressin. *Clin Pediatr* July 1993; Special Edition:28-31.

Manufactured by
rPr RHÔNE-POULENC RORER

RHÔNE-POULENC RORER PHARMACEUTICALS INC.

500 ARCOLA ROAD
COLLEGEVILLE, PA 19426
By Ferring Pharmaceuticals, Malmö, Sweden

©1994 Rhône-Poulenc Rorer Pharmaceuticals Inc.

9/94

FC#94-L69

TAKE EFFECTIVE CONTROL OF BED-WETTING



- Significant improvement in number of dry nights shown in controlled studies^{1,2}
- Rapid response—substantial effect seen in as few as 1 to 3 nights of treatment³
- A combined 15-year record of successful and safe use in the U.S. and Europe⁴

Nighttime fluid intake should be restricted to decrease the potential occurrence of fluid overload; serum electrolytes should be checked at least once when therapy is continued beyond 7 days.



DDAVP[®] Nasal Spray

(desmopressin acetate) 5mL

DRY NIGHTS FOR GOOD MORNINGS

Please see brief summary of prescribing information on adjacent page.

ARCHIVES

OF

FAMILY MEDICINE

VOL 3 NO. 11, NOVEMBER 1994

Living in Medicine

The Pain

John Graham-Pole, MD, MRCP

Letters to the Editor

Headache Classification

Stephen H. Landy, MD,
Judy McGinnis, RN

**Diabetes Mellitus Management
'PENTAD'**

Frank Lawler, MD

In Reply

Claude K. Lardinois, MD

Editorial

**Assessing Consumer Expectations
and Patient Satisfaction: Passing Fad,
Mission Impossible, or 'Just What
the Doctor Ordered'?**

Jeffrey L. Susman, MD

Original Contributions

937

**The Physician's Role: Views
of the Public and the Profession
on Seven Aspects of Patient Care**

Christine A. McBride, PhD;
Daniel A. Shugars, DDS, PhD, MPH;
M. Robin DiMatteo, PhD;
Heidi S. Lepper, MA; Edward H. O'Neil, PhD;
Teresa M. Damush, MA

948

943

**Psyllium for the Reduction
of Cholestyramine-Associated
Gastrointestinal Symptoms
in the Treatment of Primary
Hypercholesterolemia**

James J. Maciejko, MS, PhD;
Ronald Brazg, MD; Ajay Shah, MD;
Sanjay Patil, MD; Melvyn Rubenfire, MD

955

943

944

945

**Patients' Interpretation
of Qualitative Probability Statements**

Kimberley Koons Woloshin, MD;
Mack T. Ruffin IV, MD, MPH;
Daniel W. Gorenflo, PhD

961

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 O. Lundberg, MD

Editor-in-Chief, Scientific
Publications

Robert L. Kennett

Vice President, Publishing

Michael D. Springer

Associate Publisher

Nawin Gupta, PhD

Director, Publishing Operations
Division

Cheryl Iverson

Director, Editorial Processing
Division

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. **AMA Physician Recruitment Advertising Department:** Carri Lynch, Supervisor, 800-262-2260.



SB SmithKline Beecham
Pharmaceuticals

Philadelphia, PA 19101

© SmithKline Beecham, 1994

RELAFEN[®]

NABUMETONE



Statement of Ownership, Management, and Circulation
(Required by 39 U.S.C. 3685)

1. Publication Title Archives of Family Medicine	2. Publication No. 0 0 9 - 5 0 5	3. Filing Date 9-30-94
4. Issue Frequency Monthly	5. No. of Issues Published Annually 12	6. Annual Subscription Price \$95.00

7. Complete Mailing Address of Known Office of Publication (Street, City, County, State, and ZIP+4) (Not Printer)
515 N. State Street, Chicago, IL 60610 Cook County

8. Complete Mailing Address of Headquarters or General Business Office of Publisher (Not Printer)
515 N. State Street, Chicago, IL 60610 Cook County

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor (Do Not Leave Blank)
Publisher (Name and Complete Mailing Address)
American Medical Association, 515 N. State Street, Chicago, IL 60610

Editor (Name and Complete Mailing Address)
Majorie A. Bowman, M.D., MPA, 515 N. State Street, Chicago, IL 60610

Managing Editor (Name and Complete Mailing Address)
None

10. Owner (If owned by a corporation, its name and address must be stated and also immediately thereafter the names and addresses of stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, the names and addresses of the individual owners must be given. If owned by a partnership or other unincorporated firm, its name and address as well as that of each individual must be given. If the publication is published by a nonprofit organization, its name and address must be stated.) (Do Not Leave Blank)

Full Name	Complete Mailing Address
American Medical Association	515 N. State Street, Chicago, IL 60610

11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check here. None

Full Name	Complete Mailing Address
None	

12. For completion by nonprofit organizations authorized to mail at special rates. The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes. (Check one)
 Has Not Changed During Preceding 12 Months
 Has Changed During Preceding 12 Months (If changed, publisher must submit explanation of change with this statement)

PS Form 3526, October 1994

(See Instructions on Reverse)

13. Publication Name Archives of Family Medicine	14. Issue Date for Circulation Data Below 9/94	
15. Extent and Nature of Circulation	Average No. Copies Each Issue During Preceding 12 Months	Actual No. Copies of Single Issue Published Nearest to Filing Date
a. Total No. Copies (Net Press Run)	10/93-9/94 85,879	86,513
b. Paid and/or Requested Circulation (1) Sales Through Dealers and Carriers, Street Vendors, and Counter Sales (Not Mailed)	0	0
(2) Paid or Requested Mail Subscriptions (Include Advertisers' Proof Copies/Exchange Copies)	83,939	84,151
c. Total Paid and/or Requested Circulation (Sum of 15b(1) and 15b(2))	83,939	84,151
d. Free Distribution by Mail (Samples, Complimentary, and Other Free)	0	0
e. Free Distribution Outside the Mail (Carriers or Other Means)	0	0
f. Total Free Distribution (Sum of 15d and 15e)	0	0
g. Total Distribution (Sum of 15c and 15f)	83,939	84,151
h. Copies Not Distributed (1) Office Use, Leftovers, Spoiled	1,940	2,362
(2) Return from News Agents	0	0
i. Total (Sum of 15g, 15h(1), and 15h(2))	83,939	86,513
Percent Paid and/or Requested Circulation (15c / 15g x 100)	100%	100%

16. This Statement of Ownership will be printed in the 11/94 issue of this publication. Check box if not required to publish.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner
V.P. - Publishing October 11, 1994

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including multiple damages and civil penalties).

Instructions to Publishers

- Complete and file one copy of this form with your postmaster on or before October 1, annually. Keep a copy of the completed form for your records.
- Include in items 10 and 11, in cases where the stockholder or security holder is a trustee, the name of the person or corporation for whom the trustee is acting. Also include the names and addresses of individuals who are stockholders who own or hold 1 percent or more of the total amount of bonds, mortgages, or other securities of the publishing corporation. In item 11, if none, check box. Use blank sheets if more space is required.
- Be sure to furnish all information called for in item 15, regarding circulation. Free circulation must be shown in items 15d, e, and f.
- If the publication had second-class authorization as a general or requester publication, this Statement of Ownership, Management, and Circulation must be published; it must be printed in any issue in October or the first printed issue after October, if the publication is not published during October.
- In item 16, indicate date of the issue in which this Statement of Ownership will be printed.
- Item 17 must be signed.

Failure to file or publish a statement of ownership may lead to suspension of second-class authorization.

PS Form 3526, October 1994 (Reverse)

ARCHIVES

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:
Vicky Golden
Senior Copy Editor/Atex Specialist:
Paul Frank
Copy Editors:
Diane L. Cannon
Gwen Chaffen
Mary E. Coerver
Vonda L. Meltesen
Manuscript Records Clerk:
Tonja Glover

Specialty Journal Division Office

Administrative Assistant:
Marla Hall

Electronic Production Department

Director: Jaye Matthews
Electronic Production Supervisor:
Linda Knott
Electronic Production Operators:
Gail Barrett
Brenda Chandler-Haynes
Michael L. Culbert
Leslie Koch
Mary Ann Kuranda
Sandra Lopez
Graphics Manager:
Charl Richey-Davis
Graphics Operators:
Regina Vander Reyden
JoAnne Weiskopf
Alicja Wojcik
Manager, Proofreading:
Teresa H. Omiotek
Proofreaders:
David Antos
Brenda J. Gregoline
Daniel James
Mary Kay Tinerella
Production Assistant:
Melanie Parenti

Publishing Operations Division

Assistant Division Director:
Mary C. Steermann
Production Assistant: Valerie Balkcom

Distribution

Distribution Manager: Paul Gasielko

Database & New Media

Electronic Coordinator:
Mary Ellen Johnston
Database Assistant: Peter Watkins
Indexing Associate: George Kruto

**Advertising & Production
Department**

Director: Vanessa Hayden
Paper & Planning: Diane Darnell
Manager, Advertising Services:
Carole Piszker
Manager, Production Services:
Susan Price
Production Associates:
Karen Adams-Taylor
Betty Frigerio
Anita Jackson
Debbie Pogorzelski
Sarah Powell
Jennifer Reiling
Christine M. Wagenknecht
E. Ruth White

Production Assistant: Jo Anne Turner

**Publishing Operations Division
Office Staff**

Manager, Budgets & Costs:
Bonnie Van Clevon
Office Manager:
Karen Branham

**Circulation Processing
Department**

Director: Beverly Martin

**Licensing & Permissions
Department**

Director: Norman Frankel
Permissions: Laslo Hunyadi

Reprints

Reprint Coordinator: Joseph Reklash



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

FOR HYPERTENSION OR ANGINA

Rx
Cardizem CD
Start with one
180-mg
capsule daily

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 $24\% \pm 6\%$) 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 dermatological 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 (i.e., 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: Patechiae, 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

ccc06493a

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

American Medical Association

Physicians dedicated to the health of America



Affordable Patient Education Introducing the AMA Healthy Heart Series

Today, physicians think twice about using high priced educational materials. Yet informing patients about the risk factors of heart disease is vital to their health.

The solution – the AMA's new Healthy Heart Series. Features 4 magazine style booklets and 4 attention getting videos, all for a price that won't break your budget. Use them alone or in tandem. AMA member discounts apply. 30 day money back guarantee.



- Guide To Stop Smoking
- Guide To Your Healthy Heart
- Guide To High Blood Pressure Control
- Guide To Controlling Your Cholesterol

For more information and free booklet sample
Call Toll Free (800) 432-8433

Distributed by: Milner-Fenwick, Inc.
2125 Greenspring Dr., Timonium, MD 21093

MA-05

Have a question...



with your subscription to an American Medical Association publication? **Call 1-800-AMA-2350.** FAX 312-464-5831. Our Subscriber Services Center is ready to help you. Just call. Your questions can be answered in minutes.

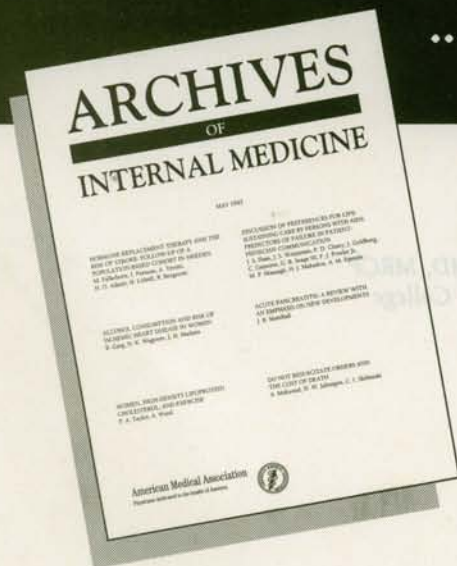
American Medical Association

Physicians dedicated to the health of America



Keep in touch

...with Internal Medicine and the subspecialties



Make Archives of Internal Medicine your first choice for new medical information. One of the world's best-read and most frequently cited journals in its field, Archives of Internal Medicine's clinical relevance is widely acknowledged. And now more than ever, Archives makes the best use of your reading time.

- **Important medical information**
Original studies, timely reviews and commentaries.
- **Thorough peer review and stringent standards**
Ensures that selected articles meet the highest scientific standards.
- **Practical new design**
Saves you time.
- **Twice-monthly frequency**
Brings the latest findings to you faster and makes each issue easier for you to quickly review. 24 issues for only \$115.

Now published twice each month!

Call toll-free 1-800-AMA-2350.

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.

Usage in 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 cirrhosis, 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.

Latent 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 spasms 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, bulous 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 tight containers as defined in USP. See product circular for full prescribing information.

Revised: 5/83

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

RP RHÔNE-POULENC RORER
RHÔNE-POULENC RORER PHARMACEUTICALS INC.
500 ARCOLA ROAD
COLLEGEVILLE, PA 19382

©1994 Rhône-Poulenc Rorer Pharmaceuticals Inc.

FC#94-R52

I N T R O D U C I N G



THE COUGH LIQUIDATOR

Cough relief designed to make remaining coughs more productive.

Now, help relieve dry, hacking coughs and make the most of remaining coughs with new Brontex—the codeine formula with the most guaifenesin.

3 times more guaifenesin per tablet than a teaspoon of other codeine brands.*

Only new Brontex combines 10 mg codeine—the most commonly prescribed level of the antitussive many doctors prefer—with 300 mg guaifenesin—the expectorant with the time-proven safety profile—in a convenient, single-tablet dose.

Only Brontex exceeds the minimum therapeutic requirements for guaifenesin.

Unlike other codeine brands, new Brontex, with its convenient dosing regimen, reaches well into the daily therapeutic range for guaifenesin (1,200 mg to 2,400 mg) set by federal guidelines.



Now for dry, unproductive coughs, there's new Brontex—the codeine cough formula with the most guaifenesin.

FROM THE MAKERS OF ENTEX® PRODUCTS

NEW Brontex®

CODEINE PHOSPHATE...10mg
(Warning: May be habit forming)
GUAIFENESIN.....300mg



FEWER COUGHS, WETTER COUGHS

Please see brief summary of prescribing information on next page.

FROM THE MAKERS OF ENTEX® PRODUCTS

NEW **Brontex**®

CODEINE PHOSPHATE...10mg
(Warning: May be habit forming)
GUAIFENESIN.....300mg



Cough relief designed to make remaining coughs
more productive

Up to 3 times more guaifenesin than
other codeine brands

Exceeds the minimum therapeutic requirements
for guaifenesin set by federal guidelines

FEWER COUGHS, WETTER COUGHS

Codeine may cause sedation and have additive sedative effects with other CNS depressants.

* Recommended dosing for most codeine/guaifenesin products is two teaspoons every four hours.

Brontex®

(codeine phosphate/guaifenesin) tablets

DESCRIPTION: Each Brontex® tablet and 4 teaspoonfuls (20 mL) of Brontex liquid contains codeine phosphate.....10 mg
Warning — May be habit forming
guaifenesin.....300 mg

INDICATIONS AND USAGE: Temporarily relieves cough due to minor throat and bronchial irritation as may occur with a cold, or inhaled irritants. Helps loosen phlegm (mucus) and thin bronchial secretions to rid the bronchial passageways of bothersome mucus.

CONTRAINDICATIONS: Brontex tablets are contraindicated in patients with known hypersensitivity to any of its ingredients. Brontex tablets are contraindicated for use in patients with asthma.

WARNINGS: Codeine is not recommended for use in children under 2 years of age. Children under 2 years may be more susceptible to the respiratory depressant effects of codeine, including respiratory arrest, coma, and death.

PRECAUTIONS: General: Codeine should be used with extreme caution in patients with severe CNS depression, respiratory depression, or those prone to respiratory depression, acute alcoholism, chronic pulmonary disease and those with substantially decreased respiratory reserve. Codeine should be administered with caution in patients with acute abdominal conditions, convulsive disorders, significant hepatic or renal impairment, fever, hypothyroidism, Addison's disease, ulcerative colitis, prostatic hypertrophy, in patients with recent gastrointestinal or urinary tract surgery, and in the very young or elderly or debilitated patients.

Administration of codeine may be accompanied by histamine release and should be used with caution in children with atopy.

Dosage of codeine should not be increased if cough fails to respond; an unresponsive cough should be reevaluated in 5 days or sooner for possible underlying pathology, such as foreign body or lower respiratory tract disease. Codeine may cause or aggravate constipation.

Hypotensive Effects: Codeine may produce hypotension in ambulatory patients.

Head Injury and Increased Intracranial Pressure: The risk of respiratory depression and elevation of cerebrospinal fluid pressure is increased by opiate agonists, including codeine, in the presence of head injury, intracranial lesions, or a pre-existing increase in intracranial pressure. They also may produce adverse reactions such as sedation and pupillary changes which may obscure the clinical course of patients with head injuries.

Respiratory Conditions with Productive Cough or Chronic Respiratory Disease: The risks and benefits of opiate agonists or cough suppressants, including codeine, should be carefully considered in illness associated with productive cough or in chronic respiratory disease where interference with ability to clear the tracheobronchial tree of secretions would have a deleterious effect on the patient's respiratory function.

Information for Patients: Brontex tablets may cause marked drowsiness or may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. Ambulatory patients should be told to avoid engaging in such activities until it is known that they do not become drowsy or dizzy from Brontex tablets. Children should be supervised to avoid potential harm in bike riding or in other hazardous activities.

The concomitant use of alcohol or other central nervous system depressants, including opiate agonists, sedatives, hypnotics, and tranquilizers, may have an additive effect and should be avoided or their dosage reduced. Codeine, like other opiate agonists, may produce orthostatic hypotension in some ambulatory patients. Patients should be cautioned accordingly.

Drug Interactions: Caution should be used when taking this product with CNS depressants including alcohol, sedatives, tranquilizers and drugs used for depression, especially monoamine oxidase inhibitors (MAOIs). These combinations may cause greater sedation than is caused by the products used alone.

Drug/Laboratory Test Interactions: Guaifenesin has been reported to interfere with clinical laboratory determinations of urinary 5-hydroxyindoleacetic acid (5-HIAA) and urinary vanillylmandelic acid (VMA). Because opiate agonists may increase biliary tract pressure, with resultant increases in plasma amylase or lipase levels, determination of these enzyme levels may be unreliable for 24 hours after an opiate agonist has been given.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies with Brontex tablets in animals to evaluate carcinogenic, mutagenic, or impairment of fertility potential have not been conducted. Studies conducted by the National Toxicology Program with codeine in rats and mice to evaluate its carcinogenic potential are in progress.

Pregnancy:

Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with Brontex tablets. It is also not known whether Brontex tablets can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Brontex tablets should be given to a pregnant woman only if clearly needed.

Studies with codeine in hamsters and mice to evaluate its developmental toxicity potential have been reported by the National Toxicology Program. Codeine produced a decrease in mean fetal weight in both hamsters and mice, but did not produce structural malformations.

Nonteratogenic Effects: Dependence has been reported in newborns whose mothers took opiates regularly during pregnancy. Signs of withdrawal include irritability, excessive crying, tremors, hyperreflexia, fever, vomiting, and diarrhea. These

signs usually disappear during the first few days of life.

Labor and Delivery: Use should be avoided during labor and delivery. Opiates cross the placental barrier. The closer to delivery and the larger the dose used, the greater the possibility of respiratory depression in the newborn. If the mother received opiates during labor, the newborn should be closely observed for signs of respiratory depression. Resuscitation, and in severe cases, naloxone may be required. Codeine may also prolong labor.

Nursing Mothers: Codeine is excreted in breast milk in amounts that are probably insignificant when given at usual therapeutic dose. It is not known whether guaifenesin is excreted in breast milk. Caution should be exercised when Brontex tablets are administered to a nursing mother. The possibility of clinically important amounts of codeine being excreted in breast milk in individuals abusing codeine should be considered.

Pediatric Use: Brontex tablets are not recommended for use in children below the age of 12 years. Brontex liquid is not recommended for use in children below the age of 6 years.

ADVERSE REACTIONS:

Nervous System: CNS depression, particularly respiratory depression, light-headedness, dizziness, sedation, euphoria, dysphoria, headache, transient hallucination, disorientation, visual disturbances, and convulsions.

Cardiovascular: Tachycardia, bradycardia, palpitation, faintness, syncope, orthostatic hypotension (common to opiate agonists), and circulatory depression.

Gastrointestinal: Nausea, vomiting, stomach pain, constipation, and biliary tract spasm. Patients with chronic ulcerative colitis may experience increased colonic motility; in patients with acute ulcerative colitis, toxic dilation has been reported.

Genitourinary: Oliguria and urinary retention; antidiuretic effect has been reported (common to opiate agonists).

Allergic: Infrequent pruritus, urticaria, angioneurotic edema, laryngeal edema, and rare anaphylactic reaction.

Other: Flushing of the face, sweating, and weakness.

DRUG ABUSE AND DEPENDENCE: Brontex tablets are a Schedule III Controlled Substance. Brontex liquid is a Schedule V controlled substance.

Codeine is known to be subject to abuse; however, the abuse potential of oral codeine is lower than that of most other opiate agonists because of its lower potency at therapeutic doses. However, codeine must be administered only under close supervision to patients with a history of drug abuse or dependence.

Psychological dependence, physical dependence, and tolerance are known to occur with codeine.

OVERDOSAGE:

Signs and Symptoms: Serious overdose with codeine is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, miosis (mydriasis may occur in terminal necrosis or hypoxia), skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdose, apnea, circulatory collapse, cardiac arrest and death may occur.

Treatment: The treatment of overdose should provide symptomatic and supportive care. Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation as necessary. The narcotic antagonist naloxone is a specific antidote against respiratory depression resulting from overdose or unusual sensitivity to opiate agonists, including codeine. Therefore, an appropriate dose of naloxone hydrochloride (see package insert) may be administered, preferably by the intravenous route, and simultaneously with efforts at respiratory resuscitation. Since the duration of action of codeine may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated. If the amount ingested is considered dangerous or excessive, induce vomiting with ipecac syrup unless the patient is convulsing, comatose, or has lost the gag reflex, in which case perform gastric lavage using a large-bore tube. If indicated, follow with activated charcoal and a saline cathartic.

DOSAGE AND ADMINISTRATION:

Adults and children 12 years of age and older: one tablet every 4 hours.

Brontex tablets are not recommended for children under 12 years of age.

Liquid: Adults and children 12 years of age and older: 4 teaspoonfuls every 4 hours. **Children 6 to under 12 years of age:** 2 teaspoonfuls every 4 hours.

HOW SUPPLIED:

Brontex tablets are available as a red, capsule-shaped tablet, embossed "BRONTEx".

NDC 0149-0440-01 bottle of 100.

Brontex liquid is available as NDC 0149-0441-16 1 pint (473 mL) bottle.

Store at controlled room temperature (59°-86°F or 15°-30°C).

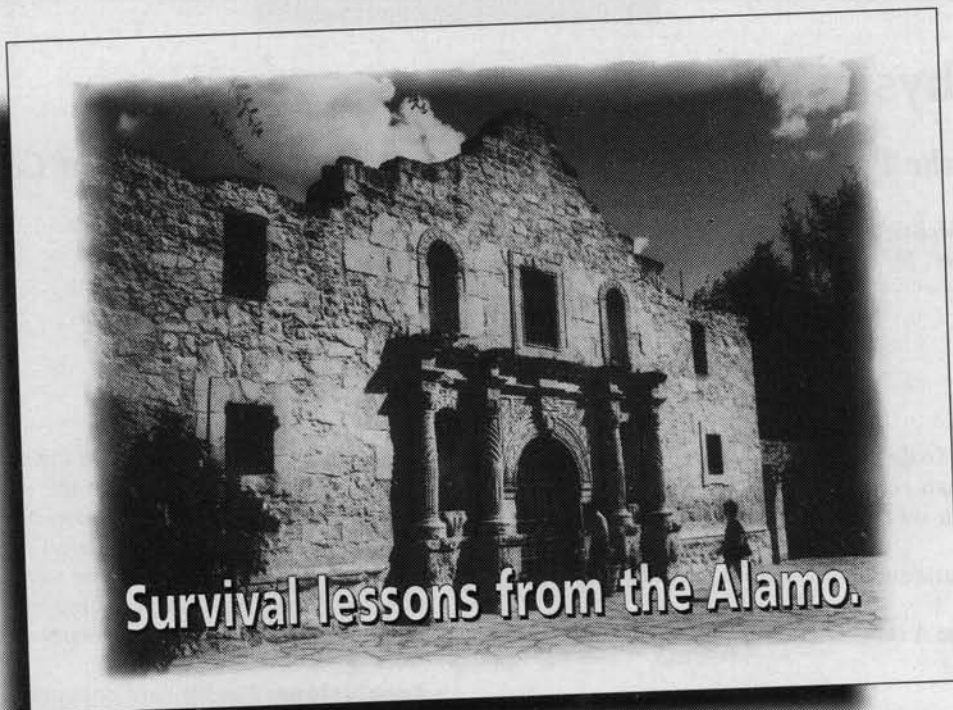
CAUTION: Federal law prohibits dispensing without prescription.

Procter & Gamble Pharmaceuticals
Cincinnati, Ohio 45202

Procter & Gamble
PHARMACEUTICALS

Patent Pending

© 1994 by Procter & Gamble 004-98 LMP 2071



Survival lessons from the Alamo.

Interactions

Medical Staff Leadership Conference — January 13-15, San Antonio, Texas

Health system reform might seem like a never-ending battle, but with leadership, vision, and perseverance, you and your medical staff can overcome any obstacle. Learn what it takes to succeed in today's rapidly changing environment. Come to *Interactions* in beautiful San Antonio, Texas, January 13-15.

Experience a new way of thinking about the future.

This year's conference, "Physician Empowerment and Teamwork in a Changing Environment," will help you experience a change of perspective on the 21st Century.

Learn how to manage change.

During *Interactions*, we will address emerging trends in health care delivery and how best to manage them. Among the trends we will discuss are:

- Physician/hospital relationships
- Economic competition
- Physician autonomy
- Resource allocation
- Regulatory constraints

Gain new leadership skills.

Special emphasis will also be placed on developing and refining your strategic planning, team building, and com-

munication skills. Each participant will learn how to be a more effective arbitrator, facilitator, manager, negotiator, problem solver, and peacemaker.

Your team leaders.

Sponsored by the *American Medical Association*, in cooperation with the *National Association Medical Staff Services* and the *Texas Medical Association*, this conference features well known experts from the health care field.

Who should attend.

The curriculum is designed to benefit experienced and newly elected or appointed medical staff leaders, including: chiefs of staff, department chairs, vice presidents of medical affairs, medical staff committee chairs, and medical staff services professionals.* Bring a team from your hospital!

For more information or to register, call **800 621-8335**.

*The AMA designates the *Interactions* conference for 18 credit hours of Category 1 of the Physician's Recognition Award of the AMA.

American Medical Association

Physicians dedicated to the health of America



Announcing

The American Medical Association

Morris Fishbein Fellowship

July 1, 1995 through
June 30, 1996



Applications are now being taken for the Morris Fishbein Fellowship in Medical Journalism sponsored by the American Medical Association. Physicians interested in making a substantial commitment to medical journalism are invited to apply for this full-time 1-year fellowship program.

Work With JAMA The successful candidate will work with the editorial and production staff of The Journal of the American Medical Association in all facets of editing and publishing a major weekly journal. At the completion of the program, it is expected that the candidate will be proficient in manuscript review and selection, issue makeup, copy editing and styling, art and layout of articles, issue planning and managing, in addition to the many other elements of journal publication. He/she will also be conversant with marketing and advertising procedures.

Publishing The candidate must have proven writing ability at the time of application, for he/she will be required during the course of the year to prepare articles for publication. Although the fellow will work under the supervision of a physician-editor, ability to work independently is a must.

Stipend A stipend of \$40,000 will be provided to the successful candidate to cover the 1-year period.

Application Forms For an application blank, please write to Richard M. Glass, MD, Deputy Editor, The Journal of the American Medical Association, 515 N State St, Chicago, IL 60610.

Deadline for Applying Completed applications should be forwarded as soon as possible and must be received no later than January 13, 1995.

Now you can depend on
Book Source, too.
It's another exclusive benefit
of your AMA membership.

Thousands of physicians depend on AMA Book Source!

Do you?

As a benefit of AMA membership **Book Source** offers thousands of titles to meet all your medical publications needs. Delivery for stock publications is prompt and reliable - getting your books to you more quickly than ordering directly from many publishers. Special orders are handled courteously and efficiently. Database searching can locate hard-to-find books.

You'll save the time and effort of calling individual publishers, and you'll save money with only one low shipping and handling fee. Major charge cards are accepted.

Won't you join your colleagues who now make **Book Source** "their source" for medical books? Available only to AMA members. Call

800 451-2262

American Medical Association

Physicians dedicated to the health of America



American Medical Association

Physicians dedicated to the health of America



Your association is giving you a new business advantage.
(We think you'll agree it's a sharp idea.)



As an American Medical Association member, you're entitled to member-only discounts on certain AT&T business long distance services, including domestic, international, and 800 Service calls.

AT&T
BUSINESS
ADVANTAGE

*A whole new way to
cut your phone bill.*

You're also entitled to the high-quality service and reliability that AT&T provides. In short, you're entitled to the AT&T Business Advantage. And it's never been easier to put it to work for your business.

Thanks to AT&T Profit By Association — an exclusive arrangement between AMA Financing & Practice Services, Inc., a subsidiary of the American Medical Association, and AT&T — you can get substantial member-only discounts simply by calling us at 1 800 367-3604 ext. 184A.

You'll also enjoy the best long distance service, the fastest connections and the most reliable network in the industry.¹ So whether you're already an AT&T customer, or you'd like to become one, take advantage of your unique status as a member. *Call 1 800 367-3604 ext. 184A and get the AT&T Business Advantage.*

AMA Financing & Practice Services, Inc.
A Subsidiary of the American Medical Association



¹Based on AT&T Bell Labs nationwide test of six major carriers' switched networks, second quarter 1993 through fourth quarter 1993. ©1994 AT&T

Read it first in...

JAMA

The Journal of the American Medical Association



Experience the power of new information with the world's leading medical journal

Each week JAMA keeps you current with:

Original Contributions: Insights into important clinical trials and research from all major medical fields.

Brief Reports: Highlights of clinical breakthroughs in convenient summary format.

Medical News and Perspectives: A weekly summary of the latest information.

Questions and Answers: Clinical questions from readers answered by distinguished specialists.

Letters: Opportunity to debate viewpoint articles and other pertinent topics.

Reviews of books, journals and software: Informed perspectives on significant new publications.

Theme Issues: Occasional issues focus entirely on a single, far-reaching topic, such as adolescent health, AIDS, violence and tobacco.

The Journal of the American Medical Association (JAMA) is one of the most clinically relevant journals available to medical professionals.

Look to JAMA as the source for:

- **Scientific Authority.** JAMA is a major source of citations in leading scientific journals and publications worldwide.
- **Comprehensive Coverage.** No other publication provides such broad coverage of the clinical and non-clinical issues in medicine.
- **Peer Opinions.** Practicing physicians, researchers, academicians and other health care professionals use JAMA to stay in touch with the concerns and attitudes of the medical profession.

The most widely read, peer reviewed journal in the world.

Yes! Please enter my one-year subscription to JAMA (48 issues) for \$115.

Name _____ MD/DO _____ Other _____
Please Print Please Specify

Address _____

City _____ State _____ Zipcode _____

Check enclosed payable to the American Medical Association.

Debit my: Visa Mastercard American Express Optima

Card No. _____ Exp. _____

Signature _____

Subscription rate for delivery outside the United States is \$190; rate includes Canadian GST.
Rates subject to change.

Mail to:
American Medical Association
Subscription Dept
515 North State Street
Chicago, IL 60610

fracture is located from the metacarpal neck, the lower the acceptable amount of angulation (Figure 6, right). Fractures at the base of the fifth metacarpal, while less common, will require orthopedic pinning to achieve satisfactory stability.

The advantage of splinting a fifth metacarpal fracture rather than circumferential casting is that splinting eliminates many of the risks associated with a circumferential cast. Patients who are involved in altercations and sustain this injury are frequently intoxicated. Should the patient be noncompliant with instructions on care of a circumferential cast, neurovascular supply to the extremity may be compromised. This is particularly true if the patient falls asleep while intoxicated and allows the arm to hang down shortly after the circumferential cast has been applied.

In evaluation of any fifth metacarpal injury, special care must be given to anyone who has a concomitant laceration near the fifth MCP joint. An attacking clenched fist may contact the mouth of the other fighter and the fifth MCP joint space may be entered by a tooth. Since the MCP joint is superficial, joint injury is easily incurred. If

not immediately identified, a septic arthritis of the MCP joint may ensue, with potential problems of osteomyelitis and residual osteoarthritis. All lacerations over the fifth MCP joint should be considered to be human bites until proven otherwise and aggressively treated with early orthopedic evaluation, frequently including operative exploration and débridement. A low threshold of suspicion is necessary since many of these patients will have no recollection of the injury or will deliberately lie about the nature of the injury.

CONCLUSIONS

The five hand fractures that are discussed in this article are common injuries that will be seen in an office setting. By understanding those circumstances for each problem that will require orthopedic intervention or specialized treatment, the family physician can totally treat the majority of these fractures. The factors that are likely to be more difficult complications include displaced or irreducible fractures, intra-articular fracture with large fragments, comminuted fractures, and those with associated neurovascular or tendon injury.

Accepted for publication June 23, 1994.

Correspondence to Family Practice Residency Program, Saint Margaret Memorial Hospital, 815 Freeport Rd, Pittsburgh, PA 15215 (Dr Schaffer).

REFERENCES

1. Culver JE, Anderson TE. Fractures of the hand and wrist in the athlete. *Clin Sports Med.* 1992; 2:101-128.
2. O'Brien ET. Fractures of the hand and wrist region. In: Rockwood CA, Wilkins KI, King RE, eds. *Fractures in Children.* 3rd ed. Philadelphia, Pa: JB Lippincott; 1991:324-326.
3. Vetter WL. How I manage mallet finger. *Physician Sports Med.* 1989;17:140-144.
4. Green DP, Rowland SA. Fractures and dislocations in the hand. In: Rockwood CA, Green DP, Buchholz RW, eds. *Fractures in Adults.* 3rd ed. Philadelphia, Pa: JB Lippincott; 1991;1:444-452, 485-494.
5. Hoffman DF, Schaffer TC. Management of common finger injuries. *Am Fam Physician.* 1991; 43:1594-1607.
6. Mintz LJ. Nail bed and crush injuries of the hand. In: Letts RM, ed. *Management of Pediatric Fractures.* New York, NY: Churchill Livingstone Inc; 1994:441-450.
7. Vicar AJ. Proximal interphalangeal joint dislocations without fractures. *Hand Clin North Am.* 1988; 4:5-13.
8. Coleman DA. Metacarpal and phalangeal fractures. *Top Emerg Med.* 1988;10:39-64.

The 1995 National Political Education Conference

Save this date!

September 27-28, 1995
The Mayflower Hotel
Washington, DC

American Medical Association

Physicians dedicated to the health of America



Encouragement

This message could be one of encouragement to you and, perhaps, certain of your patients.

Paget's disease of bone — not the rare disease it was once thought to be — is treatable in most cases. The earlier it is detected the more responsive to treatment it is likely to be. And detection can usually be accomplished with a few simple, non-invasive procedures.

Like many primary care physicians, you may feel uncomfortable treating Paget's disease because of little past experience. If so, write or call us for comprehensive, up-to-date information about the disease and its diagnosis and treatment. Alternatively, ask for our extensive referral list of specialists.

You may be able to offer someone a new lease on life. Or at least, encouragement.

The Paget's Disease Foundation, Inc.

200 Varick 3, New York, NY 10014
(212) 229-1582 • Fax (212) 229-1502

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