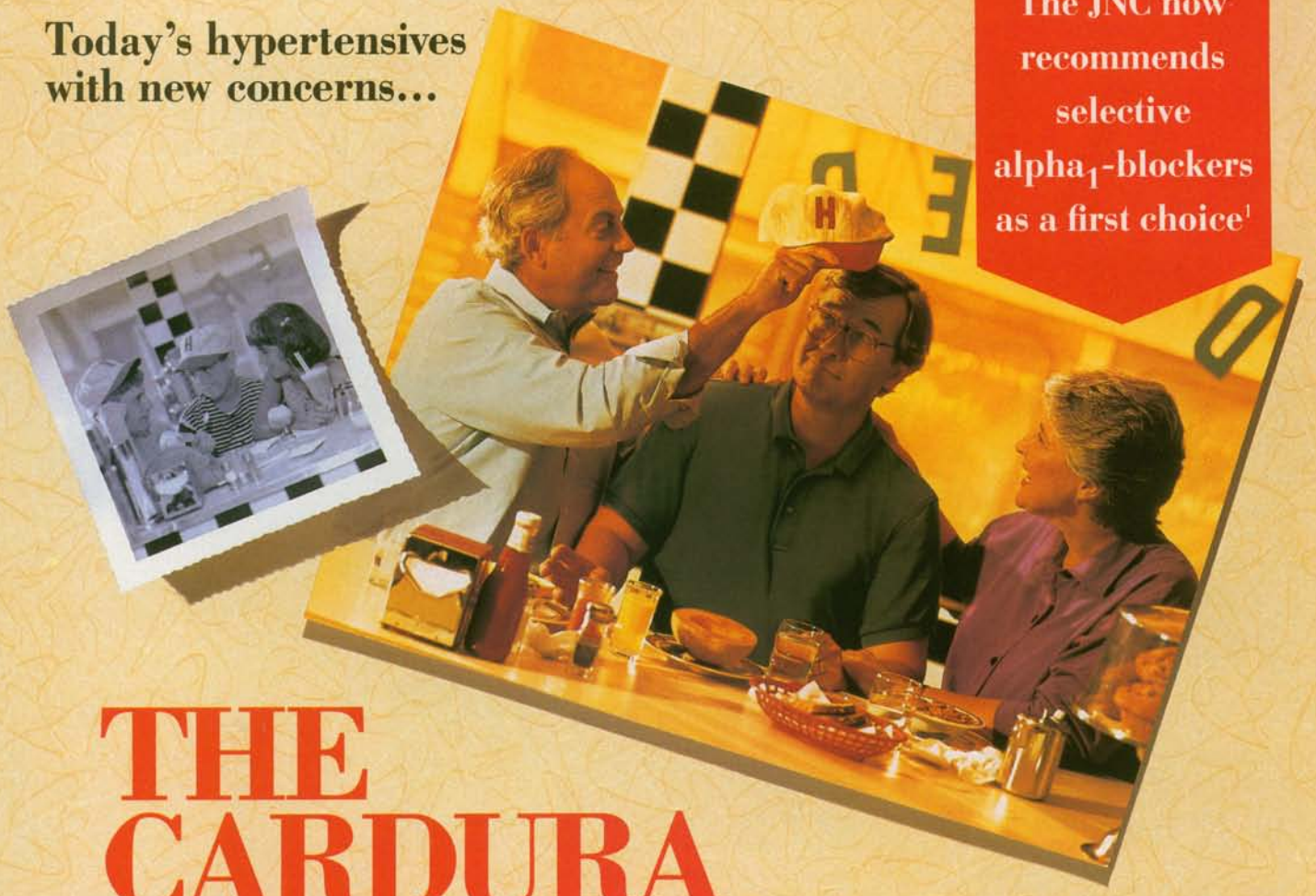
Today's hypertensives with new concerns...

The JNC now recommends selective alpha$_1$-blockers as a first choice[1]



THE CARDURA GENERATION

Choose CARDURA: first-line therapy for a new generation of hypertensives.

Choose CARDURA for around-the-clock blood pressure control that doesn't jeopardize blood lipids or blood sugar.[2-4]

CARDURA is well tolerated. In placebo-controlled studies, only three common side effects were reported significantly more often than with placebo: dizziness, somnolence, and fatigue. These were generally mild and transient. Only 2% of patients discontinued therapy due to adverse effects— the same as with placebo. Syncope has been reported, but rarely (<1%).

ONCE-A-DAY

CARDURA®

(doxazosin mesylate) Scored Tablets 1 mg, 2 mg, 4 mg, 8 mg

HYPERTENSION CONTROL FOR A NEW GENERATION.

Please see brief summary of prescribing information on next page.

ONCE-A-DAY

CARDURA®

(doxazosin mesylate) Scored Tablets 1 mg, 2 mg, 4 mg, 8 mg

References: 1. The fifth report of the Joint National Committee (JNC) on the Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). Presented to the National High Blood Pressure Education Program Coordinating Committee; June 25, 1992. **2.** Pickering TG, Hypertension and Lipid Trial Study Group. The use of 24-hour ambulatory monitoring in the assessment of antihypertensive therapy. Presented at the American Academy of Family Physicians 43rd Annual Assembly; September 24-29, 1991; Washington, D.C. **3.** The Treatment of Mild Hypertension Research Group. The Treatment of Mild Hypertension Study: a randomized, placebo-controlled trial of a nutritional-hygienic regimen along with various drug monotherapies. *Arch Intern Med.* 1991;151:1413-1423. **4.** Lehtonen A, the Finnish Multicenter Study Group. Lowered levels of serum insulin, glucose, and cholesterol in hypertensive patients during treatment with doxazosin. *Curr Ther Res.* 1990;47:278–284.

CARDURA® (doxazosin mesylate) Tablets
Brief Summary of Prescribing Information

INDICATIONS AND USAGE

CARDURA (doxazosin mesylate) is indicated for the treatment of hypertension. CARDURA may be used alone or in combination with diuretics or beta-adrenergic blocking agents. There is limited experience with CARDURA in combination with angiotensin converting enzyme inhibitors or calcium channel blockers.

CONTRAINDICATIONS

CARDURA is contraindicated in patients with a known sensitivity to quinazolines (e.g. prazosin, terazosin).

WARNINGS

Syncope and "First-dose" Effect:

Doxazosin, like other alpha-adrenergic blocking agents, can cause marked hypotension, especially in the upright position, with syncope and other postural symptoms such as dizziness. Marked orthostatic effects are most common with the first dose but can also occur when there is a dosage increase, or if therapy is interrupted for more than a few days. To decrease the likelihood of excessive hypotension and syncope, it is essential that treatment be initiated with the 1 mg dose. The 2, 4, and 8 mg tablets are not for initial therapy. Dosage should then be adjusted slowly (see DOSAGE AND ADMINISTRATION section) with increases in dose every two weeks. Additional antihypertensive agents should be added with caution.

Patients being titrated with doxazosin should be cautioned to avoid situations where injury could result should syncope occur.

In an early investigational study of the safety and tolerance of increasing daily doses of doxazosin in normotensives beginning at 1 mg/day, only 2 of 6 subjects could tolerate more than 2 mg/day without experiencing symptomatic postural hypotension. In another study of 24 healthy normotensive male subjects receiving initial doses of 2 mg/day of doxazosin, seven (29%) of the subjects experienced symptomatic postural hypotension between 0.5 and 6 hours after the first dose necessitating termination of the study. In this study 2 of the normotensive subjects experienced syncope. Subsequent trials in hypertensive patients always began doxazosin dosing at 1 mg/day resulting in a 4% incidence of postural side effects at 1 mg/day with no cases of syncope.

In multiple dose clinical trials involving over 1500 patients with dose titration every one to two weeks, syncope was reported in 0.7% of patients. None of these events occurred at the starting dose of 1 mg and 1.2% (8/664) occurred at 16 mg/day.

If syncope occurs, the patient should be placed in a recumbent position and treated supportively as necessary.

PRECAUTIONS

General

1. Orthostatic Hypotension:

While syncope is the most severe orthostatic effect of CARDURA, other symptoms of lowered blood pressure, such as dizziness, lightheadedness, or vertigo, can occur, especially at initiation of therapy or at the time of dose increases. These were common in clinical trials, occurring in up to 23% of all patients treated and causing discontinuation of therapy in about 2%.

In placebo controlled titration trials orthostatic effects were minimized by beginning therapy at 1 mg per day and titrating every two weeks to 2, 4, or 8 mg per day. There was an increased frequency of orthostatic effects in patients given 8 mg or more, 10%, compared to 5% at 1-4 mg and 3% in the placebo group.

Patients in occupations in which orthostatic hypotension could be dangerous should be treated with particular caution.

If hypotension occurs, the patient should be placed in the supine position and, if this measure is inadequate, volume expansion with intravenous fluids or vasopressor therapy may be used. A transient hypotensive response is not a contraindication to further doses of CARDURA.

2. Impaired liver function:

CARDURA should be administered with caution to patients with evidence of impaired hepatic function or to patients receiving drugs known to influence hepatic metabolism (see CLINICAL PHARMACOLOGY). There is no controlled clinical experience with CARDURA in patients with these conditions.

3. Leukopenia/Neutropenia:

Analysis of hematologic data from patients receiving CARDURA in controlled clinical trials showed that the mean WBC (N=474) and mean neutrophil counts (N=419) were decreased by 2.4% and 1.0% respectively, compared to placebo, a phenomenon seen with other alpha blocking drugs. A search through a data base of 2400 patients revealed 4 in which drug-related neutropenia could not be ruled out. Two had a single low value on the last day of treatment. Two had stable, non-progressive neutrophil counts in the 1000/mm³ range over periods of 20 and 40 weeks. In cases where follow-up was available the WBCs and neutrophil counts returned to normal after discontinuation of CARDURA. No patients became symptomatic as a result of the low WBC or neutrophil counts.

Information for Patients:

Patients should be made aware of the possibility of syncopal and orthostatic symptoms, especially at the initiation of therapy, and urged to avoid driving or hazardous tasks for 24 hours after the first dose, after a dosage increase, and after interruption of therapy when treatment is resumed. They should be cautioned to avoid situations where injury could result should syncope occur during initiation of doxazosin therapy. They should also be advised of the need to sit or lie down when symptoms of lowered blood pressure occur, although these symptoms are not always orthostatic, and to be careful when rising from a sitting or lying position. If dizziness, lightheadedness, or palpitations are bothersome they should be reported to the physician, so that dose adjustment can be considered. Patients should also be told that drowsiness or somnolence can occur with doxazosin, requiring caution in people who must drive or operate heavy machinery.

Drug Interactions:

Most (98%) of plasma doxazosin is protein bound. *In vitro* data in human plasma indicate that CARDURA has no effect on protein binding of digoxin, warfarin, phenytoin or indomethacin. There is no information on the effect of other highly plasma protein bound drugs on doxazosin binding. CARDURA has been administered without any evidence of an adverse drug interaction to patients receiving thiazide diuretics, beta blocking agents, and nonsteroidal anti-inflammatory drugs.

Drug/Laboratory test interactions:

None known.

Cardiac Toxicity in Animals:

An increased incidence of myocardial necrosis or fibrosis was displayed by Sprague-Dawley rats after 6 months of dietary administration at concentrations calculated to provide 80 mg doxazosin/kg/day and after 12 months of dietary administration at concentrations calculated to provide 40 mg doxazosin/kg/day (150 times the maximum recommended human dose assuming a patient weight of 60 kg). Myocardial fibrosis was observed in both rats and mice treated in the same manner with 40 mg doxazosin/kg/day for 18 months. No cardiotoxicity was observed at lower doses (up to 10 or 20 mg/kg/day, depending on the study) in either species. These lesions were not observed after 12 months of oral dosing in dogs and Wistar rats at maximum doses of 20 mg/kg/day and 100 mg/kg/day, respectively. There is no evidence that similar lesions occur in humans.

Carcinogenesis, Mutagenesis and Impairment of Fertility:

Chronic dietary administration (up to 24 months) of doxazosin mesylate at maximally tolerated concentrations (highest dose 40 mg/kg: about 150 times the maximum recommended human dose of 16 mg/60 kg) revealed no evidence of carcinogenicity in rats. There was also no evidence of carcinogenicity in a similarly conducted study (up to 18 months of dietary administration) in mice. The mouse study, however, was compromised by the failure to use a maximally tolerated dose of doxazosin.

Mutagenicity studies revealed no drug- or metabolite-related effects at either chromosomal or subchromosomal levels.

Studies in rats showed reduced fertility in males treated with doxazosin at oral doses of 20 (but not 5 or 10) mg/kg/day, about 75 times the maximum recommended human dose. This effect was reversible within two weeks of drug withdrawal.

Pregnancy

Teratogenic Effects, Pregnancy Category B. Studies in rabbits and rats at daily oral doses of up to 40 and 20 mg/kg, respectively (150 and 75 times the maximum recommended daily dose of 16 mg, assuming a patient weight of 60 kg), have revealed no evidence of harm to the fetus. The rabbit study, however, was compromised by the failure to use a maximally tolerated dose of doxazosin. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CARDURA should be used during pregnancy only if clearly needed.

Radioactivity was found to cross the placenta following oral administration of labelled doxazosin to pregnant rats.

Nonteratogenic Effects. In peri-postnatal studies in rats, postnatal development at maternal doses of 40 or 50 mg/kg/day of doxazosin was delayed as evidenced by slower body weight gain and a slightly later appearance of anatomical features and reflexes.

Nursing Mothers

Studies in lactating rats given a single oral dose of 1 mg/kg of [2-^{14}C]-doxazosin indicate that doxazosin accumulates in rat breast milk with a maximum concentration about 20 times greater than the maternal plasma concentration. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CARDURA is administered to a nursing mother.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

CARDURA has been administered to approximately 4000 patients, of whom 1679 were included in the clinical development program. In that program, minor adverse effects were frequent, but led to discontinuation of treatment in only 7% of patients. In placebo-controlled studies adverse effects occurred in 49% and 40% of patients in the doxazosin and placebo groups, respectively, and led to discontinuation in 2% of patients in each group. The major reasons for discontinuation were postural effects (2%), edema, malaise/fatigue, and some heart rate disturbance, each about 0.7%.

In controlled clinical trials directly comparing CARDURA to placebo there was no significant difference in the incidence of side effects, except for dizziness (including postural), weight gain, somnolence and fatigue / malaise. Postural effects and edema appeared to be dose related.

The prevalence rates presented below are based on combined data from placebo-controlled studies involving once daily administration of doxazosin at doses ranging from 1-16 mg. Table 1 summarizes those adverse experiences (possibly/probably related) reported for patients in these studies where the prevalence rate in the doxazosin group was at least 0.5% or where the reaction is of particular interest.

TABLE 1
ADVERSE REACTIONS DURING PLACEBO CONTROLLED STUDIES

		DOXAZOSIN (N=339)	PLACEBO (N=336)
CARDIOVASCULAR:	Dizziness	19%	9%
	Vertigo	2%	1%
	Postural Hypotension	0.3%	0%
	Edema	4%	3%
	Palpitation	2%	3%
	Arrhythmia	1%	0%
	Hypotension	1%	0%
	Tachycardia	0.3%	1%
	Peripheral Ischemia	0.3%	0%
SKIN APPENDAGES:	Rash	1%	1%
	Pruritus	1%	1%
MUSCULOSKELETAL:	Arthralgia/Arthritis	1%	0%
	Muscle Weakness	1%	0%
	Myalgia	1%	0%
CENTRAL & PERIPHERAL N.S.:	Headache	14%	16%
	Paresthesia	1%	1%
	Kinetic Disorders	1%	0%
	Ataxia	1%	0%
	Hypertonia	1%	0%
	Muscle Cramps	1%	0%
AUTONOMIC:	Mouth Dry	2%	2%
	Flushing	1%	0%
SPECIAL SENSES:	Vision Abnormal	2%	1%
	Conjunctivitis/Eye Pain	1%	1%
	Tinnitus	1%	0.3%
PSYCHIATRIC:	Somnolence	5%	1%
	Nervousness	2%	2%
	Depression	1%	1%
	Insomnia	1%	1%
	Sexual Dysfunction	2%	1%
GASTROINTESTINAL:	Nausea	3%	4%
	Diarrhea	2%	3%
	Constipation	1%	1%
	Dyspepsia	1%	1%
	Flatulence	1%	1%
	Abdominal Pain	0%	2%
	Vomiting	0%	1%
RESPIRATORY:	Rhinitis	3%	1%
	Dyspnea	1%	1%
	Epistaxis	1%	0%
URINARY:	Polyuria	2%	0%
	Urinary Incontinence	1%	0%
	Micturation Frequency	0%	2%
GENERAL:	Fatigue/Malaise	12%	6%
	Chest Pain	2%	2%
	Asthenia	1%	1%
	Face Edema	1%	0%
	Pain	2%	2%

Additional adverse reactions have been reported, but these are, in general, not distinguishable from symptoms that might have occurred in the absence of exposure to doxazosin. The following adverse reactions occurred with a frequency of between 0.5% and 1%: syncope, hypoesthesia, increased sweating, agitation, increased weight. The following additional adverse reactions were reported by <0.5% of 3960 patients who received doxazosin in controlled or open, short- or long-term clinical studies, including international studies. *Cardiovascular System:* angina pectoris, myocardial infarction, cerebrovascular accident; *Autonomic Nervous System:* pallor; *Metabolic:* thirst, gout, hypokalemia; *Hematopoietic:* lymphadenopathy, purpura; *Reproductive System:* breast pain; *Skin Disorders:* alopecia, dry skin, eczema; *Central Nervous System:* paresis, tremor, twitching, confusion, migraine, impaired concentration; *Psychiatric:* paroniria, amnesia, emotional lability, abnormal thinking, depersonalization; *Special Senses:* parosmia, earache, taste perversion, photophobia, abnormal lacrimation; *Gastrointestinal System:* increased appetite, anorexia, fecal incontinence, gastroenteritis; *Respiratory System:* bronchospasm, sinusitis, coughing, pharyngitis; *Urinary System:* renal calculus; *General Body System:* hot flushes, back pain, infection, fever/rigors, decreased weight, influenza-like symptoms.

CARDURA has not been associated with any clinically significant changes in routine biochemical tests. No clinically relevant adverse effects were noted on serum potassium, serum glucose, uric acid, blood urea nitrogen, creatinine or liver function tests. CARDURA has been associated with decreases in white blood cell counts (See Precautions).

OVERDOSAGE

No data are available in regard to overdosage in humans.

The oral LD_{50} of doxazosin is greater than 1000 mg/kg in mice and rats. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of fluid. As doxazosin is highly protein bound, dialysis would not be indicated.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED. The initial dosage of CARDURA in hypertensive patients is 1 mg given once daily. This starting dose is intended to minimize the frequency of postural hypotension and first dose syncope associated with CARDURA. Postural effects are most likely to occur between 2 and 6 hours after a dose. Therefore blood pressure measurements should be taken during this time period after the first dose and with each increase in dose. Depending on the individual patient's standing blood pressure response (based on measurements taken at 2-6 hours postdose and 24 hours postdose), dosage may then be increased to 2 mg and thereafter if necessary to 4 mg, 8 mg and 16 mg to achieve the desired reduction in blood pressure. **Increases in dose beyond 4 mg increase the likelihood of excessive postural effects including syncope, postural dizziness/vertigo, postural hypotension. At a titrated dose of 16 mg once daily the frequency of postural effects is about 12% compared to 3% for placebo.**

HOW SUPPLIED

CARDURA (doxazosin mesylate) is available as colored tablets for oral administration. Each tablet contains doxazosin mesylate equivalent to 1 mg (white), 2 mg (yellow), 4 mg (orange) or 8 mg (green) of the active constituent, doxazosin.

CARDURA® TABLETS are available as 1 mg (white), 2 mg (yellow), 4 mg (orange) and 8 mg (green) scored tablets.

Bottles of 100: 1 mg (NDC 0049-2750-66), 2 mg (NDC 0049-2760-66), 4 mg (NDC 0049-2770-66), 8 mg (NDC 0049-2780-66)

Recommended Storage: Store below 86°F(30°C).

CAUTION: Federal law prohibits dispensing without prescription.

65-4538-00-0 Issued Nov 1990

Pfizer Roerig

For Your Protection: The OSHA Regulations on Bloodborne Pathogens

OSHA TRAINING KIT AGAIN AVAILABLE FROM AMERICAN MEDICAL TELEVISION AND THE AMERICAN MEDICAL ASSOCIATION

The regulations on bloodborne pathogens, issued by the Occupational Safety and Health Administration (OSHA) last year, continue to change the way health care facilities cope with occupational hazards to their employees. Educating and training health care workers are key elements. A comprehensive training program produced by American Medical Television in conjunction with the American Medical Association, will help the physician, clinics and hospitals comply with the OSHA requirement to train staff in the material covered under these regulations.

Available in kit format, **For Your Protection: The OSHA Regulations on Bloodborne Pathogens** includes everything the practicing physician and his or her staff need to comply with the OSHA regulations on bloodborne pathogens plus the mandatory Hepatitis B Vaccine Declination.

Training materials include:

25-minute VHS Videocassette - Covers relevant portions of the OSHA Standards as they apply to most health care facilities, including the physician's office.

Administrator's Guide - Shows the physician or office administrator how to use the training program. The Guide also includes a copy of the amended OSHA Standards. Learn how to train employees, answer questions, and prepare necessary exposure control plans.

Model Exposure Control Plan - Designed to help any health care facility develop their own written procedures, as required by the OSHA Standard. This simple, easy-to-follow format provides a step-by-step approach for compliance, dramatically reducing the time required to develop these written procedures.

Five Training Manuals - Provide back-up reference for employees, reinforcing material presented on the videocassette.

For Your Protection: The OSHA Regulations on Bloodborne Pathogens training kit is the *only* OSHA kit reviewed for accurate medical and scientific content by the American Medical Association.

Completion of this training program has also been designated by the AMA as a Continuing Medical Education activity, worth 2 credit hours of Category 1 of the Physician Recognition Award of the AMA.

The complete **For Your Protection: The OSHA Regulations on Bloodborne Pathogens** training kit is available for $195, including S & H ($150 for AMA Members, Hospitals, Institutions, Universities, and Government Offices).

To order call **1-800-398-CNBC.**

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References: 1. Carr AA, Bottini PB, Prisant LM, et al. Once-daily verapamil in the treatment of mild-to-moderate hypertension: a double-blind placebo-controlled dose-ranging study. *J Clin Pharmacol*. 1991;31:144-150,490. 2. Further analysis of Carr AA, et al. (See reference 1.) Data on file. Lederle Laboratories, Pearl River, NY. 3. VERELAN Prescribing Information.

VERELAN

EXCELLENT TOLERABILITY SIMILAR TO PLACEBO IN A DOUBLE-BLIND STUDY[1,2]

Incidence of side effects commonly associated with calcium channel blockers

Side effect	VERELAN clinical trials[3] (n=285)	Double-blind, placebo-controlled study* VERELAN (n=81)	Placebo (n=26)
Constipation	7.4%	9.9%	11.5%
Headache	5.3%	7.4%	11.5%
Dizziness	4.2%	2.5%	3.8%
Edema	1.4%	3.7%	3.8%

**Results of a 4-week, double-blind, placebo-controlled study of patients with essential hypertension. VERELAN 120 mg/day, n = 28; 240 mg/day, n = 27; 480 mg/day, n = 26; placebo, n = 26.*

☐ *No patients discontinued VERELAN therapy due to constipation, headache, dizziness, or edema*

Constipation, which can easily be managed in most patients, is the most frequently reported side effect of verapamil.

Please see brief summary of Prescribing Information including CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS on adjacent page.

ONCE-A-DAY

VERELAN®

Verapamil HCl 120 mg 180 mg 240 mg

PELLET-FILLED CAPSULES

ARCHIVES OF FAMILY MEDICINE

VOL 2 NO. 3, MAR 1993

Living in Medicine

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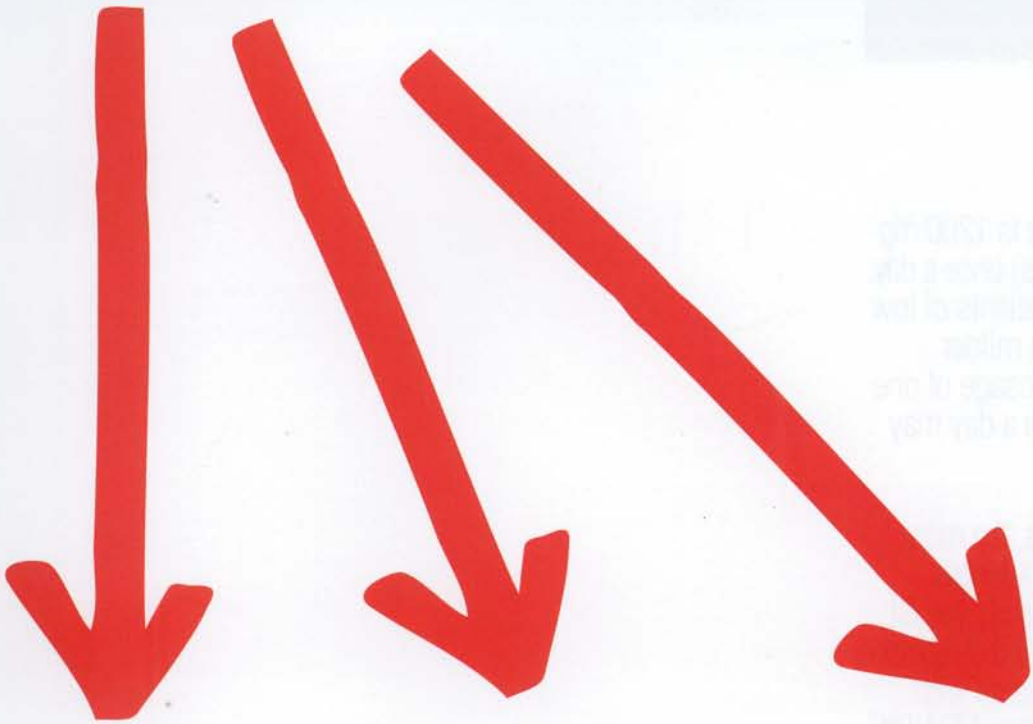
In osteoarthritis and rheumatoid arthritis

what you want in an NSAID*



☐ **Efficacy**

☐ **Tolerability**

☐ **Once-a-day dosing**

How to get it?

* Nonsteroidal anti-inflammatory drug.

Get

*Usual adult dosage is 1200 mg (two 600-mg caplets) once a day. For osteoarthritis patients of low body weight or with milder disease, an initial dosage of one 600-mg caplet once a day may be appropriate.

†As with all NSAIDs, the most frequently reported adverse reactions were related to the GI tract: nausea (8%) and dyspepsia (8%). In patients treated with DAYPRO, as with other NSAIDs in the long-term, serious GI toxicity such as bleeding, ulceration, and perforation can occur and patients should be selected accordingly.

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

SEARLE

All you

New **Two caplets, once a day ***

DAYPRO™

(oxaprozin) 600-mg caplets

Efficacy
From the same chemical class as naproxen and ibuprofen, but with the extended duration of action of piroxicam[1]

Tolerability
GI tolerability† without a loss of therapeutic efficacy[1]

Once-a-day dosing
Usual adult dosage is 1200 mg/day (two 600-mg caplets)*

want in an NSAID

Get New DAYPRO™ (oxaprozin) 600-mg caplets

All you want in an NSAID

✔ Usual adult dosage is 1200 mg (two 600-mg caplets) once a day*

Experience with NSAIDs has shown that starting therapy with maximal doses in elderly patients or those with CHF, hepatic impairment, or mild-to-moderate renal insufficiency is likely to increase the frequency of adverse events and is not recommended.

*For osteoarthritis patients of low body weight or with milder disease, an initial dosage of one 600-mg caplet once a day may be appropriate.

BRIEF SUMMARY

CONTRAINDICATIONS: Patients with previously demonstrated hypersensitivity to oxaprozin or any of its components or in individuals with the complete or partial syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). Severe and occasionally fatal asthmatic and anaphylactic reactions have been reported in patients receiving NSAIDs, and there have been rare reports of anaphylaxis in patients taking oxaprozin.

WARNINGS: RISK OF GASTROINTESTINAL (GI) ULCERATION, BLEEDING, AND PERFORATION WITH NONSTEROIDAL ANTI-INFLAMMATORY DRUG THERAPY: Serious GI toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Although minor upper GI problems, such as dyspepsia, are common, and usually develop early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs, even in the absence of previous GI tract symptoms. In patients observed in clinical trials for several months to 2 years, symptomatic upper GI ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3 to 6 months, and in about 2% to 4% of patients treated for 1 year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur. Patients at risk for developing peptic ulceration and bleeding are those with a prior history of serious GI events, alcoholism, smoking, or other factors known to be associated with peptic ulcer disease. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals, and most spontaneous reports of fatal GI events are in these populations. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions.

PRECAUTIONS: As with other NSAIDs, borderline elevations of one or more liver tests may occur in up to 15% of patients. These abnormalities may progress, remain essentially unchanged, or resolve with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of SGOT (AST) occurred in controlled clinical trials of Daypro in just under 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction or in whom an abnormal liver test has occurred should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with this drug. Severe hepatic reactions including jaundice have been reported with Daypro, and there may be a risk of fatal hepatitis with oxaprozin, such as has been seen with other NSAIDs. Although such reactions are rare, if abnormal liver tests persist or worsen, clinical signs and symptoms consistent with liver disease develop, or systemic manifestations occur (eosinophilia, rash, fever), Daypro should be discontinued. Well-compensated hepatic cirrhosis does not appear to alter the disposition of unbound oxaprozin, so dosage adjustment is not necessary. Caution should be observed in patients with severe hepatic dysfunction. Acute interstitial nephritis, hematuria, and proteinuria have been reported with Daypro as with other NSAIDs. Long-term administration of some NSAIDs to animals has resulted in renal papillary necrosis and other abnormal renal pathology. This was not observed with oxaprozin, but the clinical significance of this difference is unknown. A second form of renal toxicity has been seen in patients with preexisting conditions leading to a reduction in renal blood flow, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with previously impaired renal function, heart failure, or liver dysfunction, those taking diuretics, and the elderly. Discontinuation of NSAID therapy is often followed by recovery to the pretreatment state. Those patients at high risk who chronically take oxaprozin should have renal function monitored if they have signs or symptoms that may be consistent with mild azotemia, such as malaise, fatigue, or loss of appetite. As with all NSAID therapy, patients may occasionally develop some elevation of serum creatinine and BUN levels without any signs or symptoms. The pharmacokinetics of oxaprozin may be significantly altered in patients with renal insufficiency or in patients who are undergoing hemodialysis. Such patients should be started on doses of 600 mg/day, with cautious dosage increases if the desired effect is not obtained. Oxaprozin is not dialyzed because of its high degree of protein binding. Like other NSAIDs, Daypro may worsen fluid retention by the kidneys in patients with uncompensated cardiac failure due to its effect on prostaglandins. It should be used with caution in patients with a history of hypertension, cardiac decompensation, in patients on chronic diuretic therapy, or in those with other conditions predisposing to fluid retention. Oxaprozin has been associated with rash and/or mild photosensitivity in dermatologic testing. An increased incidence of rash on sun-exposed skin was seen in some patients in the clinical trials. Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up. Anemia may occur in patients receiving oxaprozin or other NSAIDs. This may be due to fluid retention, gastrointestinal blood loss, or an incompletely described effect upon erythrogenesis. Patients on long-term treatment with Daypro should have their hemoglobin or hematocrit values determined at appropriate intervals as determined by the clinical situation. Oxaprozin, like other NSAIDs, can affect platelet aggregation and prolong bleeding time. Daypro should be used with caution in patients with underlying hemostatic defects or in those who are undergoing surgical procedures where a high degree of hemostasis is needed. The side effects of NSAIDs can cause discomfort and, rarely, serious side effects, such as GI bleeding, which may result in hospitalization and even fatal outcomes. Physicians may wish to discuss with their patients the potential risks and likely benefits of Daypro treatment, particularly in less-serious conditions where treatment without Daypro may represent an acceptable alternative to both the patient and the physician. Patients receiving Daypro may benefit from physician instruction in the symptoms of the more common or serious GI, renal, hepatic, hematologic, and dermatologic adverse effects. Daypro is not known to interfere with most common laboratory tests, including tests for drugs of abuse. Concomitant administration of Daypro and aspirin is not recommended because oxaprozin displaces salicylates from plasma protein binding sites. Coadministration would be expected to increase the risk of salicylate toxicity. The anticoagulant effects of warfarin were not affected by the coadministration of 1200 mg/day of Daypro. Nevertheless, caution should be exercised when adding any drug that affects platelet function to the regimen of patients receiving oral anticoagulants. The total body clearance of oxaprozin was reduced by 20% in subjects who concurrently received therapeutic doses of cimetidine or ranitidine; no other pharmacokinetic parameter was affected. A change of clearance of this magnitude lies within the range of normal variation and is unlikely to produce a clinically detectable difference in the outcome of therapy. Subjects receiving 1200 mg Daypro qd with 100 mg metoprolol bid exhibited statistically significant but transient increases in sitting and standing blood pressures after 14 days. Therefore, as with all NSAIDs, routine blood pressure monitoring should be considered in these patients when starting Daypro therapy. The coadministration of oxaprozin and antacids, acetaminophen, or conjugated estrogens resulted in no statistically significant changes in pharmacokinetic parameters in single- and/or multiple-dose studies. The interaction of oxaprozin with lithium and cardiac glycosides has not been studied. In oncogenicity studies, oxaprozin administration for 2 years was associated with the exacerbation of liver neoplasms (hepatic adenomas and carcinomas) in male CD mice, but not in female CD mice or rats. The significance of this species-specific finding to man is unknown. Oxaprozin did not display mutagenic potential. Oxaprozin administration was not associated with impairment of fertility in male and female rats at oral doses up to 200 mg/kg/day (1180 mg/m^2); the usual human dose is 17 mg/kg/day (629 mg/m^2). However, testicular degeneration was observed in beagle dogs treated with 37.5 to 150 mg/kg/day (750 to 3000 mg/m^2) of oxaprozin for 6 months, or 37.5 mg/kg/day for 42 days, a finding not confirmed in other species. The clinical relevance of this finding is not known. Pregnancy Category C: There are no adequate or well-controlled studies in pregnant women. Teratology studies with oxaprozin were performed in mice, rats, and rabbits. In mice and rats, no drug-related developmental abnormalities were observed at 50 to 200 mg/kg/day of oxaprozin (225 to 900 mg/m^2). However, in rabbits, infrequent malformed fetuses were observed in dams treated with 7.5 to 30 mg/kg/day of oxaprozin (the usual human dosage range). Oxaprozin should be used during pregnancy only if the potential benefits justify the potential risks to the fetus. The effect of oxaprozin in pregnant women is unknown. NSAIDs are known to delay parturition, to accelerate closure of the fetal ductus arteriosus, and to be associated with dystocia. Oxaprozin is known to have caused decreases in pup survival in rat studies. Accordingly, the use of oxaprozin during late pregnancy should be avoided. Studies of oxaprozin excretion in human milk have not been conducted; however, oxaprozin was found in the milk of lactating rats. Since the effects of oxaprozin on infants are not known, caution should be exercised if oxaprozin is administered to nursing women. Safety and effectiveness of Daypro in children have not been established. No adjustment of the dose of Daypro is necessary in the elderly for *pharmacokinetic* reasons, although many elderly may need to receive a reduced dose because of low body weight or disorders associated with aging. No significant differences in the pharmacokinetic profile for oxaprozin were seen in studies in the healthy elderly. Although selected elderly patients in controlled clinical trials tolerated Daypro as well as younger patients, caution should be exercised in treating the elderly, and extra care should be taken when choosing a dose. As with any NSAID, the elderly are likely to tolerate adverse reactions less well than younger patients.

ADVERSE REACTIONS: The most frequently reported adverse reactions were related to the GI tract. They were nausea (8%) and dyspepsia (8%).

INCIDENCE GREATER THAN 1%: In clinical trials the following adverse reactions occurred at an incidence greater than 1% and are probably related to treatment. Reactions occurring in 3% to 9% of patients treated with Daypro are indicated by an asterisk(*); those reactions occurring in less than 3% of patients are unmarked: abdominal pain/distress, anorexia, constipation*, diarrhea*, dyspepsia*, flatulence, nausea*, vomiting, CNS inhibition (depression, sedation, somnolence, or confusion), disturbance of sleep, rash*, tinnitus, dysuria or frequency.

INCIDENCE LESS THAN 1%: ***Probable causal relationship:*** The following adverse reactions were reported in clinical trials at an incidence of less than 1% or were reported from foreign experience. Those reactions reported only from foreign marketing experience are in *italics*. The probability of a causal relationship exists between the drug and these adverse reactions: anaphylaxis, edema, blood pressure changes, peptic ulceration and/or GI bleeding, liver function abnormalities including *hepatitis*, stomatitis, hemorrhoidal or rectal bleeding, anemia, thrombocytopenia, leukopenia, ecchymoses, weight gain, weight loss, weakness, malaise, symptoms of upper respiratory tract infection, pruritus, urticaria, photosensitivity, blurred vision, conjunctivitis, *acute interstitial nephritis*, hematuria, renal insufficiency, decreased menstrual flow.

Causal relationship unknown: The following adverse reactions occurred at an incidence of less than 1% in clinical trials, or were suggested from marketing experience, under circumstances where a causal relationship could not be definitely established. They are listed as alerting information for the physician: palpitations, alteration in taste, sinusitis, pulmonary infections, alopecia, hearing decrease, increase in menstrual flow.

DRUG ABUSE AND DEPENDENCE: Daypro is a non-narcotic drug. Usually reliable animal studies have indicated that Daypro has no known addiction potential in humans.

OVERDOSAGE: No patient experienced either an accidental or intentional overdosage of Daypro in the clinical trials of the drug. Symptoms following acute overdose with other NSAIDs are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain and are generally reversible with supportive care. GI bleeding and coma have occurred following NSAID overdose. Hypertension, acute renal failure, and respiratory depression are rare. Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Gut decontamination may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose (5 to 10 times the usual dose). This should be accomplished via emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) with an osmotic cathartic. Forced diuresis, alkalization of the urine, or hemoperfusion would probably not be useful due to the high degree of protein binding of oxaprozin.

2/2/93 • P93DA7916V

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Reference: 1. Data on file, Searle.

A93DA7779T

IN CONCERT

A safety profile that works in concert with other antihypertensive agents

In limited controlled trials, no notable change in the nature or frequency of adverse reactions was shown when LOZOL was combined with other antihypertensives. LOZOL is well tolerated and does not adversely affect lipids.[1-4] And unlike Dyazide* or Maxzide,† there may be no increased risk of hyperkalemia when LOZOL is used in combination with ACE inhibitors.

ONCE A DAY

LOZOL®

INDAPAMIDE 2.5mg TABLETS

PERFORMS WITH CONFIDENCE

* Dyazide (triamterene-hydrochlorothiazide), a potassium-sparing diuretic, is a registered trademark of SmithKline Beecham Pharmaceuticals.

† Maxzide (triamterene-hydrochlorothiazide), a potassium-sparing diuretic, is a registered trademark of Lederle Laboratories.

Please see brief summary of prescribing information below.

LOZOL® (indapamide) **2.5 mg tablets**
BRIEF SUMMARY

INDICATIONS AND USAGE: 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 the use of recommended doses of indapamide primarily in elderly females. Symptoms were reversed by electrolyte replenishment (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).
Hyperuricemia 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. Serum concentrations of glucose should be monitored routinely during treatment with indapamide.
Calcium excretion is decreased by diuretics pharmacologically related to indapamide. Serum concentrations of calcium increased only slightly with indapamide in long-term studies of hypertensive patients. 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 II placebo-controlled studies and long-term controlled clinical trials, adverse reactions with ≥ 5% cumulative incidence: headache, dizziness, fatigue, weakness, loss of energy, lethargy, tiredness or malaise, muscle cramps or spasm or numbness of the extremities, nervousness, tension, anxiety, irritability or agitation; < 5% cumulative incidence: lightheadedness, drowsiness, vertigo, insomnia, depression, blurred vision, constipation, nausea, vomiting, diarrhea, gastric irritation, abdominal pain or cramps, anorexia, orthostatic hypotension, premature ventricular contractions, irregular heart beat, palpitations, frequency of urination, nocturia, polyuria, rash, hives, pruritus, vasculitis, impotence or reduced libido, rhinorrhea, flushing, hyperuricemia, 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. On the indapamide 2.5 mg group, over 50% of those patients returned to normal serum potassium values without intervention.
Other adverse reactions reported with antihypertensive/diuretics are intrahepatic cholestatic jaundice, sialadenitis, xanthopsia, photosensitivity, purpura, bullous eruptions, Stevens-Johnson syndrome, necrotizing angiitis, 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 room temperature. Avoid excessive heat.
Dispense in tight containers as defined in USP.
See product circular for full prescribing information. Revised: March 1992

References: 1. Beling S, Vukovich RA, Neiss ES, et al: Long-term experience with indapamide. *Am Heart J* 1983;106(1, Part 2):258-262. **2. Meyer-Sabellek W,** Gotzen R, Heitz J, et al: Serum lipoprotein levels during long-term treatment of hypertension with indapamide. *Hypertension* 1985;7(Suppl II):170-174. **3. Horgan JH,** O'Donovan A, Teo KK: Echocardiographic evaluation of left ventricular function in patients showing an anti-hypertensive and biochemical response to indapamide. *Postgrad Med J* 1981; 57(Suppl 2):64-67. **4. Scalabrino A,** Galeone F, Giuntoli F, et al: Clinical investigation on long-term effects of indapamide in patients with essential hypertension. *Curr Ther Res* 1984;35(1):17-22.

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ily physicians will play the central role in our country's health care provision system and that ways need to be found to ensure that enough patients will flow to other specialists so as to maintain the financial status quo.

Maury J. Greenberg, MD, D-ABFP
Stony Brook, NY

1. Clowe JL. Welcome to the family. *Arch Fam Med.* 1992;1:23-24.

In reply

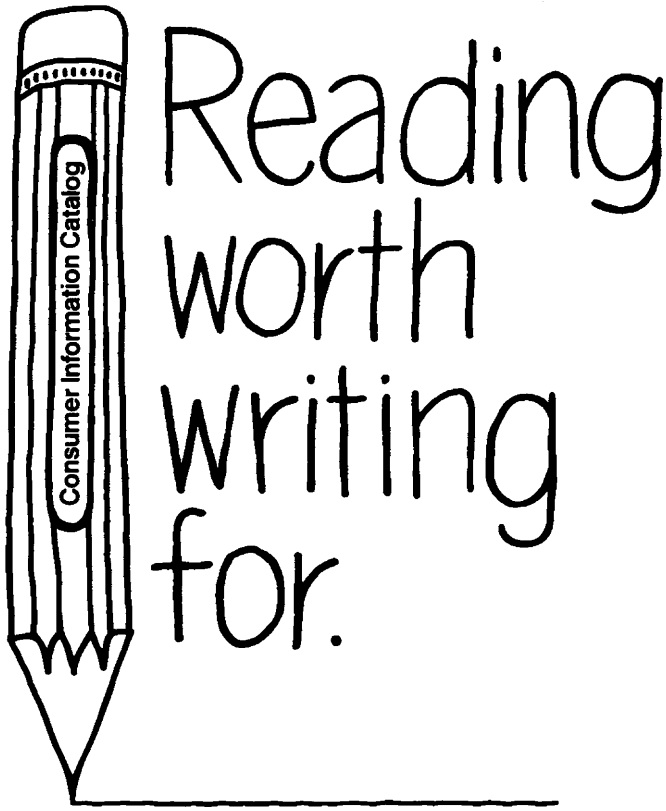
The study I described by the AMA Council on Long Range Planning and Development in cooperation with the American Academy of Family Physicians[1] identified factors that were likely to influence the future of family practice. The study findings were meant to be descriptive, not prescriptive. The fact is, fewer family physicians are including obstetrics in their practices, as the Council predicted and as was noted at the Academy's annual meeting in San Diego, Calif (American Medical News, *November 16, 1992:45). Thirty years ago, the majority of family physicians did some obstetrics; today only 25% to 30% do. This is not to say what* should *happen, merely what is happening. Liability issues have played a part, as have life-style choices and availability of obstetric training.*

My comments citing the importance of the family physician as patient advocate and case manager were not meant to "relegat[e] family physicians to the role of 'referralists.'" My point was just the opposite: that family physicians are uniquely trained and suited to provide broad-based, cost-effective care to their patients, referring to other specialists when medically appropriate. Physician specialty may indeed have an impact on resource utilization, as has been suggested recently.[2] The expertise of family physicians and others in primary care specialties is likely to be a key ingredient in health care cost reform.

Dr Greenberg is certainly correct: the scope of family practice is expanding. I hope this new ARCHIVES *will contribute to this expanding knowledge base by helping family physicians keep abreast of emerging technologies, procedures, and issues that affect their practice.*

John L. Clowe, MD
Chicago, Ill

1. American Medical Association Council on Long Range Planning and Development. *The Future of Family Practice.* Chicago, Ill: American Medical Association; 1988.
2. Greenfield S, Nelson EC, Zubkoff M, et al. Variations in resource utilization among medical specialties and systems of care: results from the Medical Outcomes Study. *JAMA.* 1992;267:1624-1630.



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Ismo® (isosorbide mononitrate) 20 mg tablets

BRIEF SUMMARY (*FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR.*)

Indications and Usage Ismo is indicated for prevention of angina pectoris due to coronary artery disease. The onset of action is not rapid enough for it to be useful in aborting an acute anginal episode.

Clinical Pharmacology Isosorbide mononitrate is the major active metabolite of isosorbide dinitrate; most of the clinical activity of the dinitrate comes from the mononitrate. Ismo is not subject to first-pass metabolism in the liver and the absolute bioavailability of isosorbide mononitrate from Ismo tablets is nearly 100%. The rate of clearance of Ismo is the same in healthy young adults, in patients with various degrees of renal, hepatic, or cardiac dysfunction, and in the elderly.

Several well-controlled studies have demonstrated that active nitrates were indistinguishable from placebo after 24 hours (or less) of continuous therapy due to the development of tolerance. Only after nitrates are absent from the body for several hours is their antianginal efficacy restored.

The drug-free interval sufficient to avoid tolerance to isosorbide mononitrate is not completely defined. The only regimen shown to avoid development of tolerance with isosorbide mononitrate involves two daily doses of Ismo tablets given 7 hours apart, so there is a gap of 17 hours between the second dose of each day and the first dose of the next day. Taking account of the relatively long half-life of isosorbide mononitrate this result is consistent with those obtained for other organic nitrates.

The same twice-daily regimen of Ismo tablets successfully avoided significant rebound/withdrawal effects. In studies of other nitrates, the incidence and magnitude of such phenomena appear to be highly dependent upon the schedule of nitrate administration.

Contraindications Allergic reactions are extremely rare, but do occur. Ismo is contraindicated in patients allergic to it.

Warnings Because the effects of Ismo are difficult to terminate rapidly and have not been established in patients with acute myocardial infarction (MI) or congestive heart failure (CHF), this drug is not recommended in these patients. If Ismo is used in these patients, careful clinical or hemodynamic monitoring is required to avoid the hazards of hypotension and tachycardia.

Precautions GENERAL Severe hypotension, particularly with upright posture, may occur with even small doses. Therefore, use with caution in patients who may be volume depleted or who are already hypotensive. Paradoxical bradycardia and increased angina pectoris may accompany Ismo-induced hypotension.

Nitrates may aggravate angina caused by hypertrophic cardiomyopathy.

INFORMATION FOR PATIENTS Tell patients they must carefully follow the prescribed dosing schedule (2 doses taken 7 hours apart) to maintain the antianginal effect (eg, take first dose on awakening and second dose 7 hours later).

Daily headaches sometimes accompany treatment with nitrates, including Ismo, and are a marker of drug activity. Patients with headaches should not alter their treatment schedule since loss of headache may be associated with simultaneous loss of antianginal efficacy. Headaches may be treated with aspirin and/or acetaminophen without affecting the antianginal activity of Ismo.

Light-headedness on standing, especially just after rising from a recumbent or seated position, may occur. This may be more frequent in patients who have consumed alcohol.

DRUG INTERACTIONS Vasodilating effects of Ismo may be additive with those of other vasodilators, especially alcohol.

Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustments of either class of agents may be necessary.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY No carcinogenic effects were observed in mice or rats exposed to oral Ismo, nor were adverse effects on rat fertility observed.

No mutagenic activity was seen in *in vitro* or *in vivo* assays.

PREGNANCY CATEGORY C Ismo has been shown to have embryocidal effects in rats and rabbits at doses at least 70 times the maximum human dose. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if potential benefit justifies potential fetal risk.

NURSING MOTHERS Excretion in human milk is unknown. Use caution if administered to a nursing woman.

PEDIATRIC USE Safety and effectiveness have not been established.

Adverse Reactions Frequency of Adverse Reactions (Discontinuations)* Occurring in >1% of Subjects

	6 Controlled U.S. Studies		92 Clinical Studies
Dose	Placebo	20 mg	(varied)
Patients	204	219	3344
Headache	9% (0%)	38% (9%)	19% (4.3%)
Dizziness	1% (0%)	5% (1%)	3% (0.2%)
Nausea, Vomiting	<1% (0%)	4% (3%)	2% (0.2%)

*Some individuals discontinued for multiple reasons

Fewer than 1% of patients reported each of the following (in many cases a causal relationship is uncertain): *Cardiovascular;* angina pectoris, arrhythmias, atrial fibrillation, hypotension, palpitations, postural hypotension, premature ventricular contractions, supraventricular tachycardia, syncope. *Dermatologic;* pruritus, rash. *Gastrointestinal;* abdominal pain, diarrhea, dyspepsia, tenesmus, tooth disorder, vomiting. *Genitourinary;* dysuria, impotence, urinary frequency. *Miscellaneous;* asthenia, blurred vision, cold sweat, diplopia, edema, malaise, neck stiffness, rigors. *Musculoskeletal;* arthralgia. *Neurologic;* agitation, anxiety, confusion, dyscoordination, hypoesthesia, hypokinesia, increased appetite, insomnia, nervousness, nightmares. *Respiratory;* bronchitis, pneumonia, upper respiratory tract infection.

Rarely, ordinary doses of organic nitrates have caused methemoglobinemia in normal-seeming patients (See **Overdosage**).

Overdosage The ill effects of overdosage are generally related to the ability of Ismo to induce vasodilation, venous pooling, reduced cardiac output and hypotension. Symptoms may include increased intracranial pressure, with any or all of persistent throbbing headache, confusion, and moderate fever; vertigo; palpitations; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhea); syncope (especially with upright posture); air hunger and dyspnea, later followed by reduced ventilatory effort; diaphoresis, with the skin either flushed or cold and clammy; heart block and bradycardia; paralysis; coma; seizures and death.

Serum levels have no role in managing overdose. The likely lethal dose in humans is unknown.

There is neither a specific antidote to Ismo overdose, nor data to suggest a means for accelerating its elimination from the body; dialysis is ineffective. Hypotension associated with Ismo overdose results from venodilatation and arterial hypovolemia; therefore, direct therapy toward an increase in central fluid volume. Use of arterial vasoconstrictors (eg, epinephrine) is likely to do more harm than good. In patients with renal disease or CHF, treatment of Ismo overdose may be difficult and require invasive monitoring.

Methemoglobinemia has occurred in patients receiving other organic nitrates, and probably could occur as a side effect of Ismo. There are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible. Suspect the diagnosis in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO_2. Classically, methemoglobinemic blood is chocolate brown, without color change on exposure to air. The treatment of choice for methemoglobinemia is methylene blue, 1-2 mg/kg intravenously.

DOSAGE AND ADMINISTRATION The recommended regimen of Ismo tablets is 20 mg (one tablet) twice daily, with the two doses given 7 hours apart. For most patients, this can be accomplished by taking the first dose on awakening and the second dose 7 hours later. This dosing regimen provides a daily nitrate-free interval to avoid the development of refractory tolerance (see **Clinical Pharmacology**).

Well-controlled studies have shown that tolerance to Ismo tablets is avoided when using the twice daily regimen in which the two doses are given 7 hours apart. This regimen has been shown to have antianginal efficacy beginning 1 hour after the first dose and lasting at least 5 hours after the second dose. The duration (if any) of antianginal activity beyond 12 hours has not been studied; large controlled studies with other nitrates suggest that no dosing regimen should be expected to provide more than 12 hours of continuous antianginal efficacy per day.

Dosage adjustments are not necessary in the elderly patients or in patients with altered renal or hepatic function.

This Brief Summary is based upon the current Ismo direction circular, CI 4127-1, Issued January 10, 1992.

A·H·ROBINS

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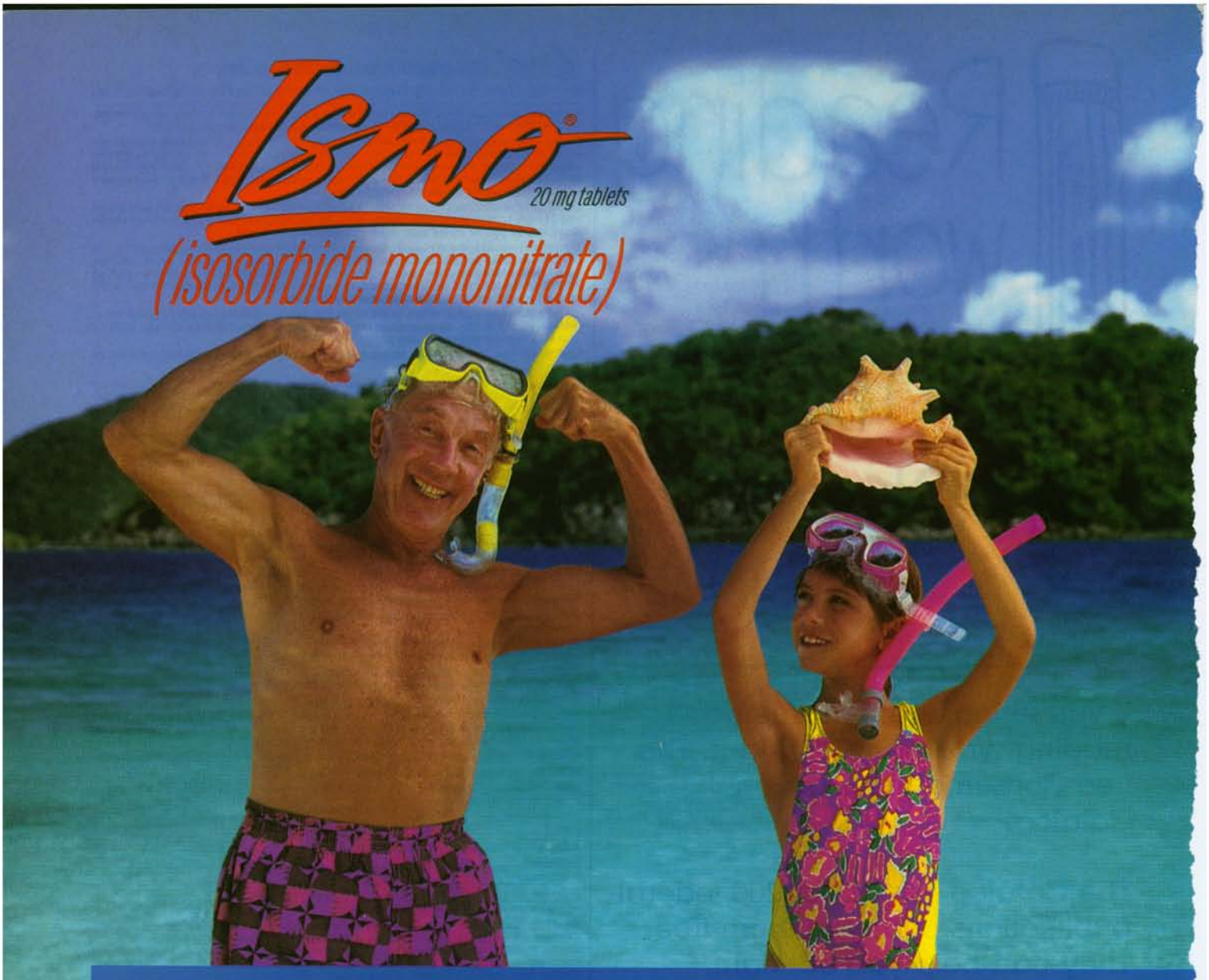
(isosorbide mononitrate)

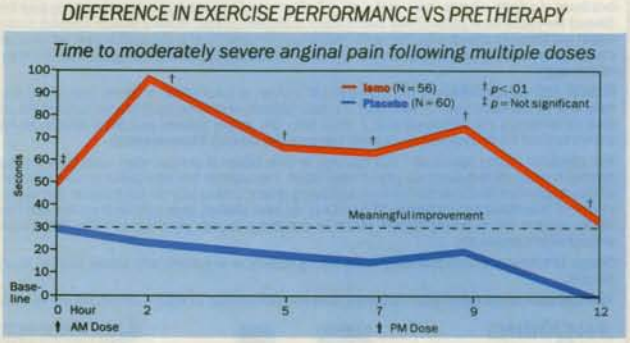


ACTIVITY YOU CAN COUNT ON

Antianginal activity for at least 12 hours*

In clinical trials, Ismo dosed at 8 AM and 3 PM for a period of 2 weeks demonstrated efficacy for at least 12 hours after the first dose, ie, 5 hours after the second dose, of each day.[1]

DIFFERENCE IN EXERCISE PERFORMANCE VS PRETHERAPY



Baseline = 7 min 3 sec

(Adapted from Protocol 12)[1]

Predictable pharmacokinetic profile

Ismo is nearly 100% bioavailable. Blood levels following oral dosage are as predictable as those seen with I.V. isosorbide mononitrate administration.[2]

Helps get active patients active again

**The dosing schedule of 20 mg, twice daily, 7 hours apart (with a 17-hour dose-free interval) must be followed carefully.*

Ismo is not recommended for use in aborting acute anginal episodes. The most common side effect, headache, may be managed with simple analgesics. As with other long-acting nitrates, Ismo is not recommended in patients with acute myocardial infarction or congestive heart failure.

References: 1. *Data on file, Wyeth-Ayerst Laboratories, Protocol 12.* **2.** *Abshagen U: Overview of the pharmacokinetics of isosorbide-5-mononitrate. In Julian DG, Rittinghausen R, Überbacher HJ, eds. Mononitrate II. New York: Springer-Verlag; 1987:pp 28-36.*

Please see brief summary of prescribing information on adjacent page.

THE PRAVACHOL® DIRECTION

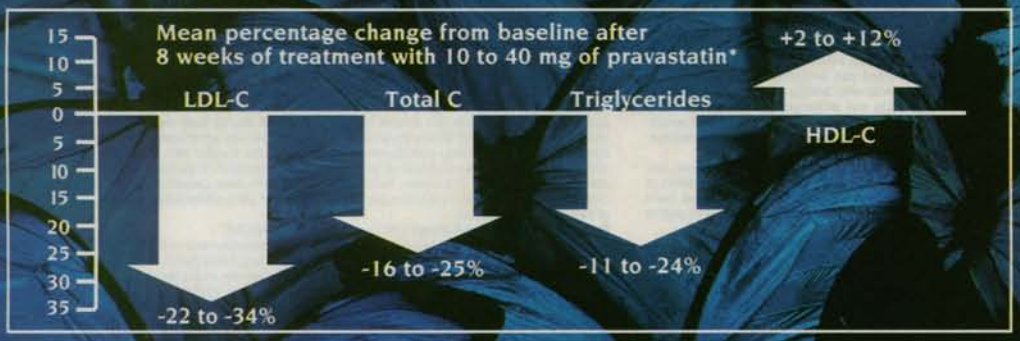
Effective lipid management doesn't have to be tough

PRAVACHOL® (pravastatin sodium) is indicated as an adjunct to diet for the reduction of elevated total and LDL-cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb) when the response to diet alone has not been adequate.

IN LIPID MANAGEMENT

Effective lipid management—improves key lipids

Significantly reduces LDL-C. Increases beneficial HDL-C.[1]



*Each arrow represents a range of means derived from a single placebo-controlled study that included 55 patients treated with pravastatin.

Excellent safety/tolerability profile for patients

- Low incidence of side effects
- Discontinuation rate from pravastatin (1.7%) was not statistically different from that of placebo (1.2%)
- Active liver disease *or* unexplained transaminase elevations, pregnancy and lactation are contraindications to the use of pravastatin

Easy dosing regimen and other patient benefits

- Usual dose: 20 mg once daily at bedtime, with or without food
- PRAVACHOL can be used confidently with many other medications

PRAVACHOL®

pravastatin sodium 20 mg tablets

Bristol-Myers Squibb Company

Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the final page of this advertisement.

Reference: 1. Jones PH, et al. Once-daily pravastatin in patients with primary hypercholesterolemia: a dose-response study. *Clin Cardiol.* 1991;14:146-151.

PRAVACHOL® (Pravastatin Sodium Tablets)

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained, persistent elevations in liver function tests (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin; the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency. A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 6α-hydroxy isomeric metabolite (SQ 31,906). A small increase was seen in mean AUC values and half life ($t_{1/2}$) for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

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

Drug Interactions: *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin:* See WARNINGS: Skeletal Muscle.

Antipyrine: Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION: Concomitant Therapy.)

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and Cmax of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine: The $AUC_{0-t/2e}$ for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin: In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SQ 31,906 and SQ 31,945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, Cmax, and Tmax for the pravastatin metabolite SQ 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with *aspirin, antacids* [1 hour prior to PRAVACHOL (pravastatin sodium)], *cimetidine, nicotinic acid,* or *probucol,* no statistically significant differences in bioavailability were seen when PRAVACHOL was administered.

Other Drugs: During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to diuretics, antihypertensives, digitalis, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced ($p<0.004$) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a ≥50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose ($p<0.01$). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls ($p<0.05$). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*; a forward mutation assay in L5178Y TK +/− mouse lymphoma cells; a chromosomal aberration test in hamster cells; and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area (mg/meter^2). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: **General.**)

ADVERSE REACTIONS

Pravastatin is generally well tolerated; adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy; this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug:

	All Events %		Events Attributed to Study Drug %	
Body System/Event	Pravastatin (N = 900)	Placebo (N = 411)	Pravastatin (N = 900)	Placebo (N = 411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

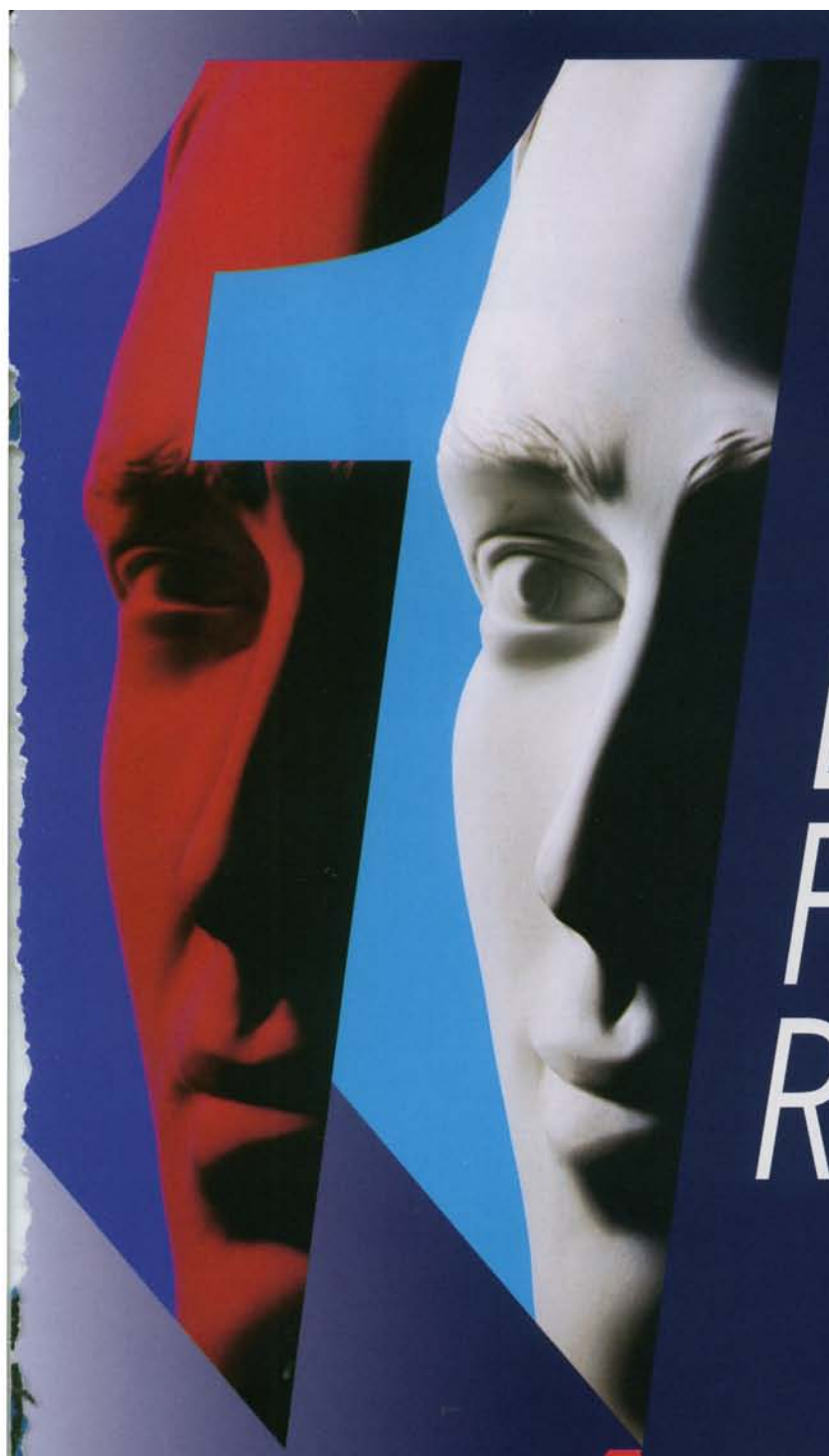
Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is **not** associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS: **Skeletal Muscle** and PRECAUTIONS: **Drug Interactions.**)

OVERDOSAGE

There have been no reports of overdoses with pravastatin.

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required.



Now, for allergic rhinitis...

ONCE DAILY FOR RELIEF

Once daily for convenience

Once daily for comfort[1,2]

Once daily for unsurpassed safety[3-5]

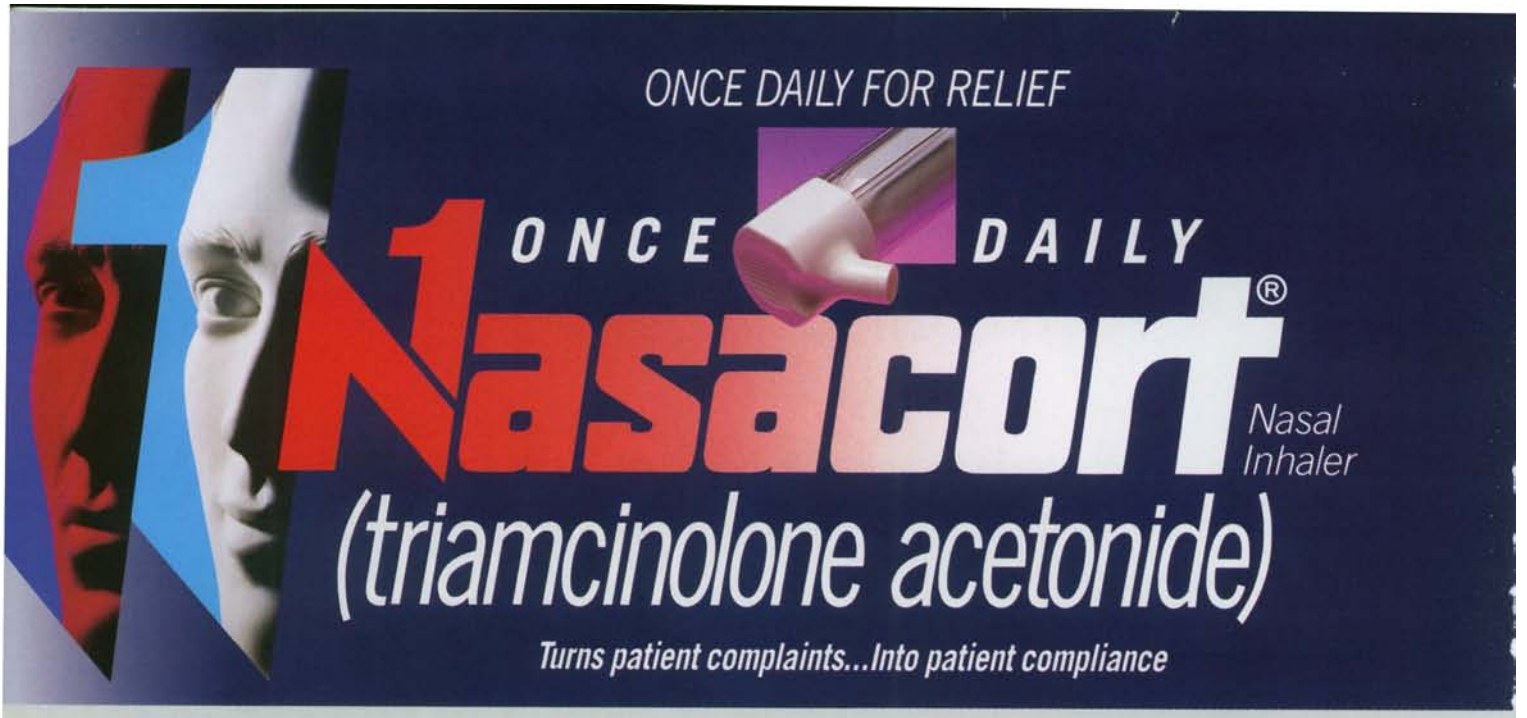
ONCE DAILY

Nasacort® Nasal Inhaler

(triamcinolone acetonide)

Turns patient complaints...Into patient compliance

Please see brief summary of prescribing information on adjacent page.



ONCE DAILY **Nasacort®** Nasal Inhaler
(triamcinolone acetonide)

For Intranasal Use Only
Shake Well Before Using

BRIEF SUMMARY

CONTRAINDICATIONS: Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS: The replacement of a systemic corticosteroid with a topical corticoid can be accompanied by signs of adrenal insufficiency and, in addition, some patients may experience symptoms of withdrawal, *e.g.*, joint and/or muscular pain, lassitude and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticoids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant doses of corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

The use of Nasacort Nasal Inhaler with alternate-day systemic prednisone could increase the likelihood of hypothalamic-pituitary-adrenal (HPA) suppression compared to a therapeutic dose of either one alone. Therefore, Nasacort Nasal Inhaler should be used with caution in patients already receiving alternate-day prednisone treatment for any disease.

PRECAUTIONS

General: In clinical studies with triamcinolone acetonide administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has rarely occurred. When such an infection develops it may require treatment with appropriate local therapy and discontinuance of treatment with Nasacort Nasal Inhaler.

Triamcinolone acetonide administered intranasally has been shown to be absorbed into the systemic circulation in humans. Patients with active rhinitis showed absorption similar to that found in normal volunteers. Nasacort at 440 mcg/day for 42 days did not measurably affect adrenal response to a six hour cosyntropin test. In the same study prednisone 10 mg/day significantly reduced adrenal response to ACTH over the same period (see CLINICAL TRIALS section).

Nasacort Nasal Inhaler should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract or in patients with untreated fungal, bacterial, or systemic viral infections or ocular herpes simplex.

Because of the inhibitory effect of corticosteroids on wound healing in patients who have experienced recent nasal septal ulcers, nasal surgery or trauma, a corticosteroid should be used with caution until healing has occurred.

When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, Nasacort Nasal Inhaler should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

Information for Patients: Patients being treated with Nasacort Nasal Inhaler should receive the following information and instructions.

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to obtain medical advice.

Patients should use Nasacort Nasal Inhaler at regular intervals since its effectiveness depends on its regular use. A decrease in symptoms may occur as soon as 12 hours after starting steroid therapy and generally can be expected to occur within a few days of initiating therapy in allergic rhinitis. The patient should take the medication as directed and should not exceed the prescribed dosage. The patient should contact the physician if symptoms do not improve after three weeks, or if the condition worsens. Nasal irritation and/or burning or stinging after use of the spray occur only rarely with this product. The patient should contact the physician if they occur.

For the proper use of this unit and to attain maximum improvement, the patient should read and follow the accompanying patient instructions carefully. Because the amount dispensed per puff may not be consistent, it is important to shake the canister well. Also, the canister should be discarded after 100 actuations.

Carcinogenesis, Mutagenesis: Animal studies of triamcinolone acetonide to test its carcinogenic potential are underway.

Impairment of Fertility: Male and female rats which were administered oral triamcinolone acetonide at doses as high as 15 mcg/kg/day (110 mcg/m^2/day, as calculated on a surface area basis) exhibited no evidence of impaired fertility. The maximum human dose, for comparison, is 6.3 mcg/kg/day (240 mcg/m^2/day). However, a few female rats which received maternally toxic doses of 8 or 15 mcg/kg/day (60 mcg/m^2/day or 110 mcg/m^2/day, respectively, as calculated on a surface area basis) exhibited dystocia and prolonged delivery.

Developmental toxicity, which included increases in fetal resorptions and stillbirths and decreases in pup body weight and survival, also occurred at the maternally toxic doses (2.5 - 15.0 mcg/kg/day or 20 - 110 mcg/m^2/day, as calculated on a surface area basis). Reproductive performance of female rats and effects on fetuses and offspring were comparable between groups that received placebo and non-toxic or marginally toxic doses (0.5 and 1.0 mcg/kg/day or 3.8 mcg/m^2/day and 7.0 mcg/m^2/day).

Pregnancy: Pregnancy Category C. Like other corticoids, triamcinolone acetonide has been shown to be teratogenic in rats and rabbits. Teratogenic effects, which occurred in both species at 0.02, 0.04 and 0.08 mg/kg/day (approximately 135, 270 and 540 mcg/m^2/day in the rat and 320, 640 and 1280 mcg/m^2/day in the rabbit, as calculated on a surface area basis), included a low incidence of cleft palate and/or internal hydrocephaly and axial skeletal defects. Teratogenic effects, including CNS and cranial malformations, have also been observed in non-human primates at 0.5 mg/kg/day (approximately 6.7 mg/m^2/day). The doses of 0.02, 0.04, 0.08, and 0.5 mg/kg/day used in these toxicology studies are approximately 12.8, 25.5, 51, and 318.7 times the minimum recommended dose of 110 mcg of Nasacort per day and 3.2, 6.4, 12.7, and 80 times the maximum recommended dose of 440 mcg of Nasacort per day based on a patient body weight of 70 kg. Administration of aerosol by inhalation to pregnant rats and rabbits produced embryotoxic and fetotoxic effects which were comparable to those produced by administration by other routes. There are no adequate and well-controlled studies in pregnant women. Triamcinolone acetonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticoids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticoids than humans. In addition, because there is a natural increase in glucocorticoid production during pregnancy, most women will require a lower exogenous steroid dose and many will not need corticoid treatment during pregnancy.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether triamcinolone acetonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when Nasacort Nasal Inhaler is administered to nursing women.

Pediatric Use: Safety and effectiveness have not been established in children below the age of 12. Oral corticoids have been shown to cause growth suppression in children and teenagers, particularly with higher doses over extended periods. If a child or teenager on any corticoid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of steroids should be considered.

ADVERSE REACTIONS: In controlled and uncontrolled studies, 1257 patients received treatment with intranasal triamcinolone acetonide. Adverse reactions are based on the 567 patients who received a product similar to the marketed Nasacort canister. These patients were treated for an average of 48 days (range 1 to 117 days). The 145 patients enrolled in uncontrolled studies received treatment from 1 to 820 days (average 332 days).

The most prevalent adverse experience was headache, being reported by approximately 18% of the patients who received Nasacort. Nasal irritation was reported by 2.8% of the patients receiving Nasacort. Other nasopharyngeal side effects were reported by fewer than 5% of the patients who received Nasacort and included: dry mucous membranes, naso-sinus congestion, throat discomfort, sneezing, and epistaxis. The complaints do not usually interfere with treatment and in the controlled and uncontrolled studies approximately 1% of patients have discontinued because of these nasal adverse effects.

In the event of accidental overdose, an increased potential for these adverse experiences may be expected, but systemic adverse experiences are unlikely (see OVERDOSAGE section).

OVERDOSAGE: Acute overdosage with this dosage form is unlikely. The acute topical application of the entire 15 mg of the canister would most likely cause nasal irritation and headache. It would be unlikely to see acute systemic adverse effects if the nasal application of the 15 mg of triamcinolone acetonide was administered all at once.

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

Please see product circular for full prescribing information.

REFERENCES: 1. Winder J, Barker J, Bell T, et al: Intranasal triamcinolone acetonide aerosol versus beclomethasone dipropionate aqueous spray in perennial allergic rhinitis. *Medical Interface* 1992;5(6, suppl):16. 2. Data on file, Rhône-Poulenc Rorer Pharmaceuticals Inc. 3. Findlay S, Huber F, Garcia J, et al: Efficacy of once-a-day intranasal administration of triamcinolone acetonide in patients with seasonal allergic rhinitis. *Ann Allergy* 1992;68(3):228-232. 4. Storms W, Bronsky E, Findlay S, et al: Once daily triamcinolone acetonide nasal spray is effective for the treatment of perennial allergic rhinitis. *Ann Allergy* 1991;66(4):329-334. 5. Feiss G, Morris R, Rom D, et al: A comparative study of the effects of intranasal triamcinolone acetonide aerosol (ITAA) and prednisone on adrenocortical function. *J Allergy Clin Immunol* 1992;89(6):1151-1156.

Marketed by:

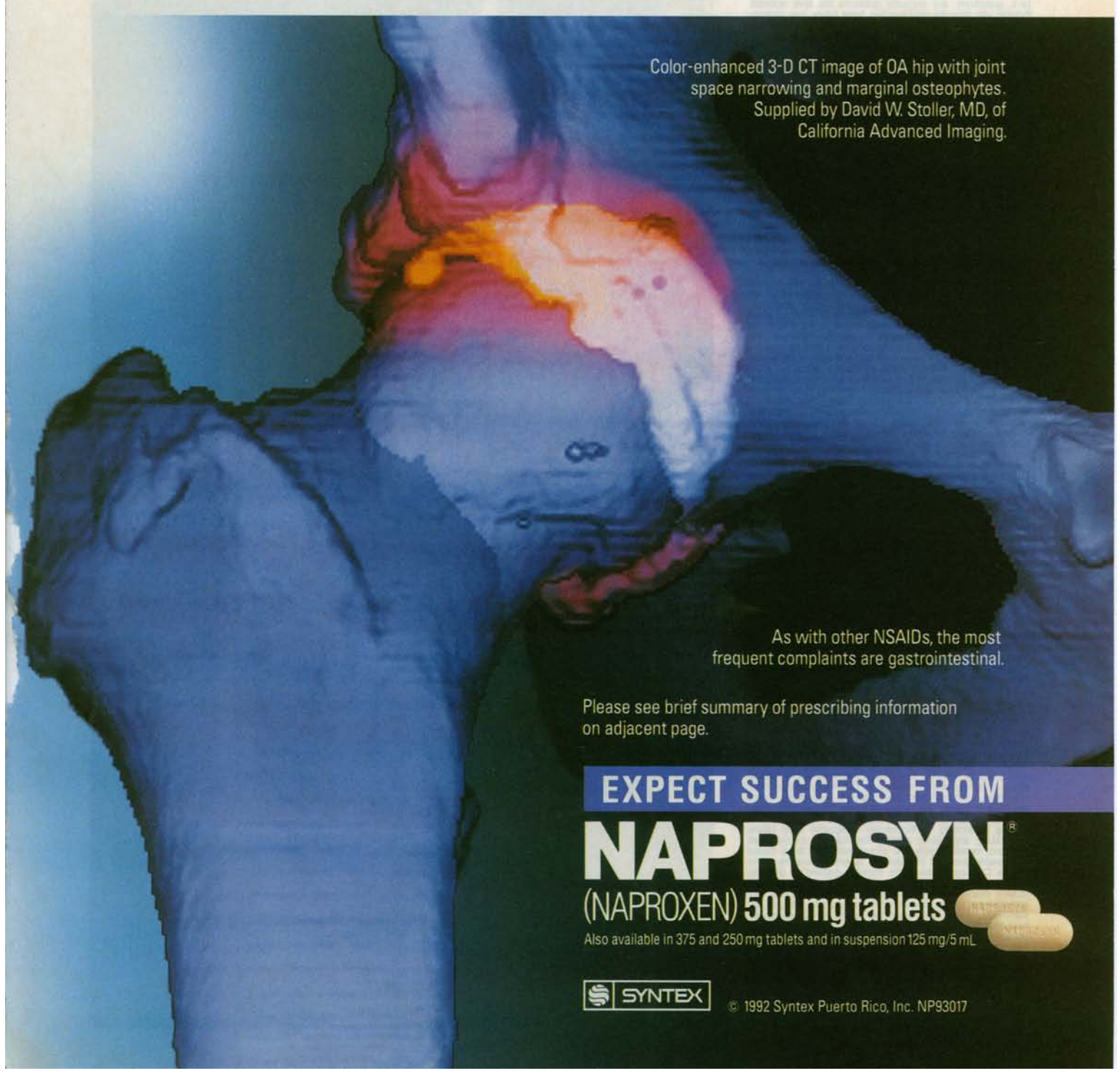
RHÔNE-POULENC RORER

RHÔNE-POULENC RORER PHARMACEUTICALS INC.
500 ARCOLA ROAD
COLLEGEVILLE, PA 19426

NA06X193(X)A 1/93 FC#93-F18 Printed in U.S.A.

FOR CHRONIC ARTHRITIS

EXPECT A REDUCTION IN JOINT PAIN AND TENDERNESS



Color-enhanced 3-D CT image of OA hip with joint space narrowing and marginal osteophytes. Supplied by David W. Stoller, MD, of California Advanced Imaging.

As with other NSAIDs, the most frequent complaints are gastrointestinal.

Please see brief summary of prescribing information on adjacent page.

EXPECT SUCCESS FROM

NAPROSYN®

(NAPROXEN) 500 mg tablets

Also available in 375 and 250 mg tablets and in suspension 125 mg/5 mL

SYNTEX

NAPROSYN®

(NAPROXEN) 500 mg tablets

Brief Summary:

Contraindications: Patients who have had allergic reactions to NAPROSYN, ANAPROX or ANAPROX DS or in whom aspirin or other NSAIDs induce the syndrome of asthma, rhinitis, and nasal polyps. Because anaphylactic reactions usually occur in patients with a history of such reactions, question patients for asthma, nasal polyps, urticaria, and hypotension associated with NSAIDs before starting therapy. If such symptoms occur, discontinue the drug. **Warnings:** Serious GI toxicity such as bleeding, ulceration, and perforation can occur at any time, with or without warning symptoms, in patients treated chronically with NSAIDs. Remain alert for ulceration and bleeding in such patients even in the absence of previous GI tract symptoms. In clinical trials, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur. Studies have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than others and most spontaneous reports of fatal GI events are in this population. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity. **Precautions:** DO NOT GIVE **NAPROSYN®** (NAPROXEN) CONCOMITANTLY WITH **ANAPROX®** (NAPROXEN SODIUM) OR **ANAPROX® DS** (NAPROXEN SODIUM) SINCE THEY BOTH CIRCULATE IN PLASMA AS THE NAPROXEN ANION. Acute interstitial nephritis with hematuria, proteinuria, and nephrotic syndrome has been reported. Patients with impaired renal function, heart failure, liver dysfunction, patients taking diuretics, and the elderly are at greater risk of overt renal decompensation. If this occurs, discontinue the drug. Use with caution and monitor serum creatinine and/or creatinine clearance in patients with significantly impaired renal function. Use caution in patients with baseline creatinine clearance less than 20 mL/minute. Use the lowest effective dose in the elderly or in patients with chronic alcoholic liver disease or cirrhosis. With NSAIDs, borderline elevations of liver tests may occur in up to 15% of patients. They may progress, remain unchanged, or be transient with continued therapy. Elevations of SGPT or SGOT occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and fatal hepatitis, have been reported rarely. If liver disease develops or if systemic manifestations occur (e.g., eosinophilia or rash), discontinue therapy. If steroid dosage is reduced or eliminated during therapy, do so slowly and observe patients closely for adverse effects, including adrenal insufficiency and exacerbation of arthritis symptoms. Determine hemoglobin values periodically for patients with initial values of 10 grams or less who receive long-term therapy. Peripheral edema has been reported. Therefore, use with caution in patients with fluid retention, hypertension or heart failure. The drug's antipyretic and anti-inflammatory activities may reduce fever and inflammation, diminishing their diagnostic value. Conduct ophthalmic studies if any change or disturbance in vision occurs. For patients with restricted sodium intake, note that the suspension contains 8 mg/mL of sodium. **Information for Patients:** Side effects of NSAIDs can cause discomfort and, rarely, there are more serious side effects, such as GI bleeding, which may result in hospitalization and even fatal outcomes. Physicians may wish to discuss with patients the potential risks and likely benefits of NSAID treatment, particularly when they are used for less serious conditions where treatment without NSAIDs may be an acceptable alternative. Patients should use caution for activities requiring alertness if they experience drowsiness, dizziness, vertigo or depression during therapy. **Laboratory Tests:** Because serious GI tract ulceration and bleeding can occur without warning symptoms, follow chronically treated patients for signs and symptoms of these and inform them of the importance of this follow-up. **Drug Interactions:** Use caution when giving concomitantly with coumarin-type anticoagulants; a hydantoin, sulfonamide or sulfonylurea; furosemide; lithium; beta-blockers; probenecid; or methotrexate. **Drug/Laboratory Test Interactions:** The drug may decrease platelet aggregation and prolong bleeding time or increase urinary values for 17-ketogenic steroids. Temporarily stop therapy for 72 hours before doing adrenal function tests. The drug may interfere with urinary assays of 5HIAA. **Carcinogenesis:** A 2-year rat study showed no evidence of carcinogenicity. **Pregnancy:** Category B. Do not use during pregnancy unless clearly needed. Avoid use during late pregnancy. **Nursing Mothers:** Avoid use in nursing mothers. **Pediatric Use:** Single doses of 2.5-5 mg/kg, with total daily dose not exceeding 15 mg/kg/day, are safe in children over 2 years of age. **Adverse Reactions:** In a study, GI reactions were more frequent and severe in rheumatoid arthritis patients on 1,500 mg/day than in those on 750 mg/day. In studies in children with juvenile arthritis, rash and prolonged bleeding times were more frequent, GI and CNS reactions about the same, and other reactions less frequent than in adults. Incidence Greater Than 1%; Probable Causal Relationship: GI: The most frequent complaints related to the GI tract: constipation,* heartburn,* abdominal pain,* nausea,* dyspepsia, diarrhea, stomatitis. CNS: headache,* dizziness,* drowsiness,* light-headedness, vertigo. Dermatologic: itching (pruritus),* skin eruptions,* ecchymoses,* sweating, purpura. Special Senses: tinnitus,* hearing disturbances, visual disturbances. Cardiovascular: edema,* dyspnea,* palpitations. General: thirst. Incidence Less Than 1%; Probable Causal Relationship: GI: abnormal liver function tests, colitis, GI bleeding and/or perforation, hematemesis, jaundice, melena, peptic ulceration with bleeding and/or perforation, vomiting. Renal: glomerular nephritis, hematuria, hyperkalemia, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis. Hematologic: agranulocytosis, eosinophilia, granulocytopenia, leukopenia, thrombocytopenia. CNS: depression, dream abnormalities, inability to concentrate, insomnia, malaise, myalgia and muscle weakness. Dermatologic: alopecia, photosensitive dermatitis, skin rashes. Special Senses: hearing impairment. Cardiovascular: congestive heart failure. Respiratory: eosinophilic pneumonitis. General: anaphylactoid reactions, menstrual disorders, pyrexia (chills and fever). Causal Relationship Unknown: Hematologic: aplastic anemia, hemolytic anemia. CNS: aseptic meningitis, cognitive dysfunction. Dermatologic: epidermal necrolysis, erythema multiforme, photosensitivity reactions resembling porphyria cutanea tarda and epidermolysis bullosa, Stevens-Johnson syndrome, urticaria. GI: non-peptic GI ulceration, ulcerative stomatitis. Cardiovascular: vasculitis. General: angioneurotic edema, hyperglycemia, hypoglycemia. **Overdosage:** May have drowsiness, heartburn, indigestion, nausea, vomiting. A few patients have had seizures. Empty stomach and use usual supportive measures. In animals 0.5 g/kg of activated charcoal reduced plasma levels of naproxen. **Caution:** Federal law prohibits dispensing without prescription. See package insert for full Prescribing Information.

*Incidence of reported reaction 3%-9%. Where unmarked, incidence less than 3%.

SYNTEX

U.S. patent nos. 3,904,682, 3,998,966 and others.

Rev. 39 September 1990

True once-daily antihypertensive control*

Proved by countless patients well controlled on ***one ISOPTIN SR tablet per day—180 mg or 240 mg—*** *with virtually no change in metabolic parameters or quality of life (total daily doses above 240 mg should be administered in divided doses).*[1]

As evidenced by well-controlled, long-term studies at more than 40 US centers. With q.d. dosing, blood pressure was controlled ***at 24 hours*** *as demonstrated by a drop in diastolic BP to target levels.*

Supported by more than ***58,000,000*** *prescriptions written for once-daily verapamil SR‡ over the past* ***6*** *years.*

ONCE-DAILY

ISOPTIN SR

(verapamil HCl) 180/240 mg Sustained-Release Tablets

knoll®
BASF Group

*Clinical effectiveness is unrelated to drug-plasma levels.
†Constipation is the most frequently reported side effect of ISOPTIN* SR and is easily managed in most patients. ISOPTIN* SR should be administered with food.
‡Verapamil SR produced by Knoll for Knoll Pharmaceutical Company and G.D. Searle & Co.

Please see back for brief summary of prescribing information.

ONCE-DAILY

ISOPTIN® SR

(verapamil HCl) Sustained-Release Tablets

Unsurpassed dosage flexibility

180 mg

The recommended starting/maintenance dose

240 mg

For patients who require a step up in dosage

120 mg

For elderly or small-stature patients who require lower doses

From the originators of verapamil

knoll

BASF Group

Knoll Pharmaceutical Company
30 North Jefferson Road
Whippany, New Jersey 07981

I2095/12-92 Printed in USA

Brief Summary of Prescribing Information

CONTRAINDICATIONS: 1) Severe left ventricular dysfunction (see WARNINGS), 2) Hypotension (less than 90 mmHg systolic pressure) or cardiogenic shock, 3) Sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker), 4) 2nd or 3rd degree AV block (except in patients with a functioning artificial ventricular pacemaker), 5) Patients with atrial flutter or atrial fibrillation and an accessory bypass tract (e.g., Wolff-Parkinson-White, Lown-Ganong-Levine syndromes), 6) Patients with known hypersensitivity to verapamil hydrochloride.

WARNINGS: Heart Failure: ISOPTIN should be avoided in patients with severe left ventricular dysfunction. Patients with milder ventricular dysfunction should, if possible, be controlled before verapamil treatment. ISOPTIN should be avoided in patients with any degree of left ventricular dysfunction if they are receiving a beta adrenergic blocker (see DRUG INTERACTIONS). **Hypotension:** ISOPTIN (verapamil HCl) may produce occasional symptomatic hypotension. **Elevated Liver Enzymes:** Elevations of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Periodic monitoring of liver function in patients receiving verapamil is therefore prudent. **Accessory Bypass Tract (Wolff-Parkinson-White):** Patients with paroxysmal and/or chronic atrial flutter or atrial fibrillation and a coexisting accessory AV pathway may develop increased antegrade conduction across the accessory pathway producing a very rapid ventricular response or ventricular fibrillation after receiving intravenous verapamil. While this has not been reported with oral verapamil, it should be considered a potential risk (see CONTRAINDICATIONS). Treatment is usually D.C.-cardioversion. **Atrioventricular Block:** The effect of verapamil on AV conduction and the SA node may cause asymptomatic 1st degree AV block and transient bradycardia. Higher degrees of AV block, while infrequent (0.8%), may require a reduction in dosage or, in rare instances, discontinuation of verapamil HCl. **Patients with Hypertrophic Cardiomyopathy (IHSS):** Although verapamil has been used in the therapy of patients with IHSS, severe cardiovascular decompensation and death have been noted in this patient population.

PRECAUTIONS: Impaired Hepatic or Renal Function: Verapamil is highly metabolized by the liver with about 70% of an administered dose excreted as metabolites in the urine. In patients with impaired hepatic function the dose should be cut to 30% of the usual dose and the patient closely monitored. In patients with impaired renal function verapamil should be administered cautiously and the patients monitored for abnormal prolongation of the PR interval or other signs of excessive pharmacological effects (see OVERDOSE). **Use in Patients with Attenuated (Decreased) Neuromuscular Transmission:** Verapamil decreases neuromuscular transmission and may prolong recovery from neuromuscular blocking agents. In patients with attenuated neuromuscular transmission lower doses of verapamil may be warranted.

Drug Interactions: Beta Blockers: Concomitant use of ISOPTIN and oral beta-adrenergic blocking agents may result in additive negative effects on heart rate, atrioventricular conduction, and/or cardiac contractility. Excessive bradycardia and AV block, has been reported. The combination should be used only with caution and close monitoring. **Digitalis:** Clinical use of verapamil in digitalized patients has shown the combination to be well tolerated. However, chronic verapamil treatment increases serum digoxin levels by 50% to 75% during the first week of therapy and this can result in digitalis toxicity. Upon discontinuation of ISOPTIN (verapamil HCl), the patient should be reassessed to avoid underdigitalization. **Antihypertensive Agents:** Verapamil administered concomitantly with oral antihypertensive agents (e.g., vasodilators, angiotensin-converting enzyme inhibitors, diuretics, alpha and beta adrenergic blockers) will usually have an additive effect on lowering blood pressure. Patients receiving these combinations should be appropriately monitored. **Antiarrhythmic Agents: Disopyramide:** Disopyramide should not be administered within 48 hours before or 24 hours after verapamil administration. **Flecainide:** Concomitant administration of flecainide and verapamil may result in additive negative inotropic effect and prolongation of atrioventricular conduction. **Quinidine:** In patients with hypertrophic cardiomyopathy (IHSS), concomitant use of verapamil and quinidine may result in significant hypotension. **Other: Nitrates:** The pharmacologic profile of verapamil and nitrates as well as clinical experience suggest beneficial interactions. **Cimetidine:** Variable results on clearance have been obtained in acute studies of healthy volunteers; clearance of verapamil was either reduced or unchanged. **Lithium:** Pharmacokinetic (lowering of serum lithium levels) and pharmacodynamic (increased sensitivity to the effects of lithium) interactions between oral verapamil and lithium have been reported. **Carbamazepine:** Verapamil therapy may increase carbamazepine concentrations and produce related side effects during combined therapy. **Rifampin:** Therapy with rifampin may markedly reduce oral verapamil bioavailability. **Phenobarbital:** Phenobarbital therapy may increase verapamil clearance. **Cyclosporin:** Verapamil therapy may increase serum levels of cyclosporin. **Anesthetic Agents:** Verapamil may potentiate the activity of neuromuscular blocking agents and inhalation anesthetics. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** There was no evidence of a carcinogenic potential of verapamil administered to rats for two years. Verapamil was not mutagenic in the Ames test. Studies in female rats did not show impaired fertility. Effects on male fertility have not been determined. **Pregnancy (Category C):** There are no adequate and well-controlled studies in pregnant women. ISOPTIN crosses the placental barrier and can be detected in umbilical vein blood at delivery. This drug should be used during pregnancy, labor and delivery, only if clearly needed. **Nursing Mothers:** ISOPTIN is excreted in human milk; therefore, nursing should be discontinued while verapamil is administered. **Pediatric Use:** Safety and efficacy of ISOPTIN in children below the age of 18 years have not been established.

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 1.4%, 2° and 3° AV block 0.8%, rash 1.2%, flushing 0.6% and elevated liver enzymes (see WARNINGS). The following reactions, reported in less than 1.0% of patients, occurred under conditions (open trials, marketing experience) where a causal relationship is uncertain; they are mentioned to alert the physician to a possible relationship: angina pectoris, atrioventricular dissociation, arthralgia and rash, blurred vision, cerebrovascular accident, chest pain, claudication, confusion, diarrhea, dry mouth, ecchymosis or bruising, equilibrium disorders, erythema multiforme, exanthema, gastrointestinal distress, gingival hyperplasia, gynecomastia, hair loss, hyperkeratosis, impotence, increased urination, insomnia, macules, muscle cramps, myocardial infarction, palpitations, paresthesia, psychotic symptoms, purpura (vasculitis), shakiness, somnolence, spotty menstruation, Steven-Johnson syndrome, sweating, syncope, urticaria.

Treatment of Acute Cardiovascular Adverse Reactions: Whenever severe hypotension or complete AV block occur following oral administration of verapamil, the appropriate emergency measures should be applied immediately, e.g., intravenously administered isoproterenol HCl, levarterenol bitartrate, atropine (all in the usual doses), or calcium gluconate (10% solution). If further support is necessary, inotropic agents (dopamine or dobutamine) may be administered. Actual treatment and dosage should depend on the severity and the clinical situation and the judgment and experience of the treating physician.

OVERDOSAGE: Treatment of overdosage should be supportive. Beta-adrenergic stimulation or parenteral administration of calcium solutions may increase calcium ion flux across the slow channel, and have been used effectively in treatment of deliberate overdosage with verapamil. Clinically significant hypotensive reactions or fixed high degree AV block should be treated with vasopressor agents or cardiac pacing, respectively. Asystole should be handled by the usual measures including cardiopulmonary resuscitation.

DOSAGE AND ADMINISTRATION

Essential Hypertension

The dose of ISOPTIN SR should be individualized by titration and the drug should be administered with food. Initiate therapy with 180 mg of sustained-release verapamil HCl, ISOPTIN SR, given in the morning. Lower, initial doses of 120 mg a day may be warranted in patients who may have an increased response to verapamil (e.g., the elderly or small people, etc.). Upward titration should be based on therapeutic efficacy and safety evaluated weekly and approximately 24 hours after the previous dose. The antihypertensive effects of ISOPTIN SR are evident within the first week of therapy.

If adequate response is not obtained with 180 mg of ISOPTIN SR, the dose may be titrated upward in the following manner:

a. 240 mg each morning.

b. 180 mg each morning plus 180 mg each evening, or 240 mg each morning plus 120 mg each evening.

c. 240 mg every twelve hours.

When switching from immediate release ISOPTIN to ISOPTIN SR, the total daily dose in milligrams may remain the same.

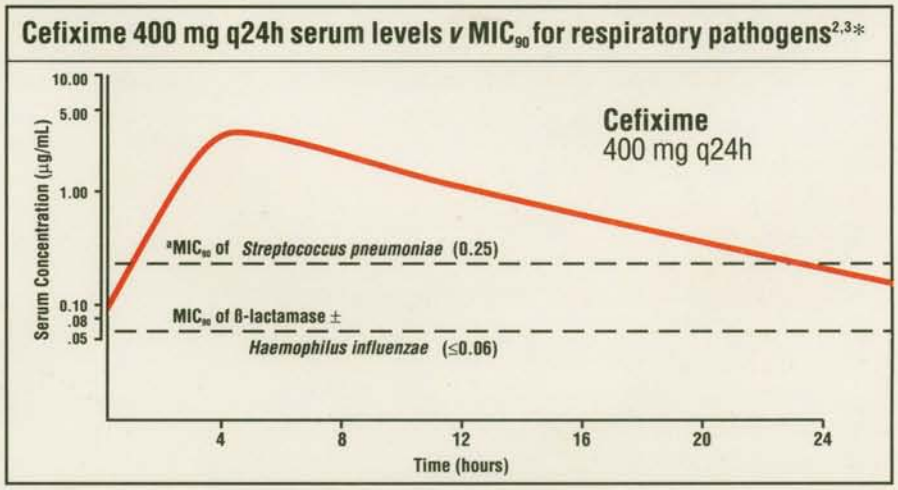
2767/2-90 Printed in U.S.A.

THE SUPRAX DIFFERENCE

SUPRAX Maintains Inhibitory Concentrations Above MIC_{90} for Virtually 24 Hours*

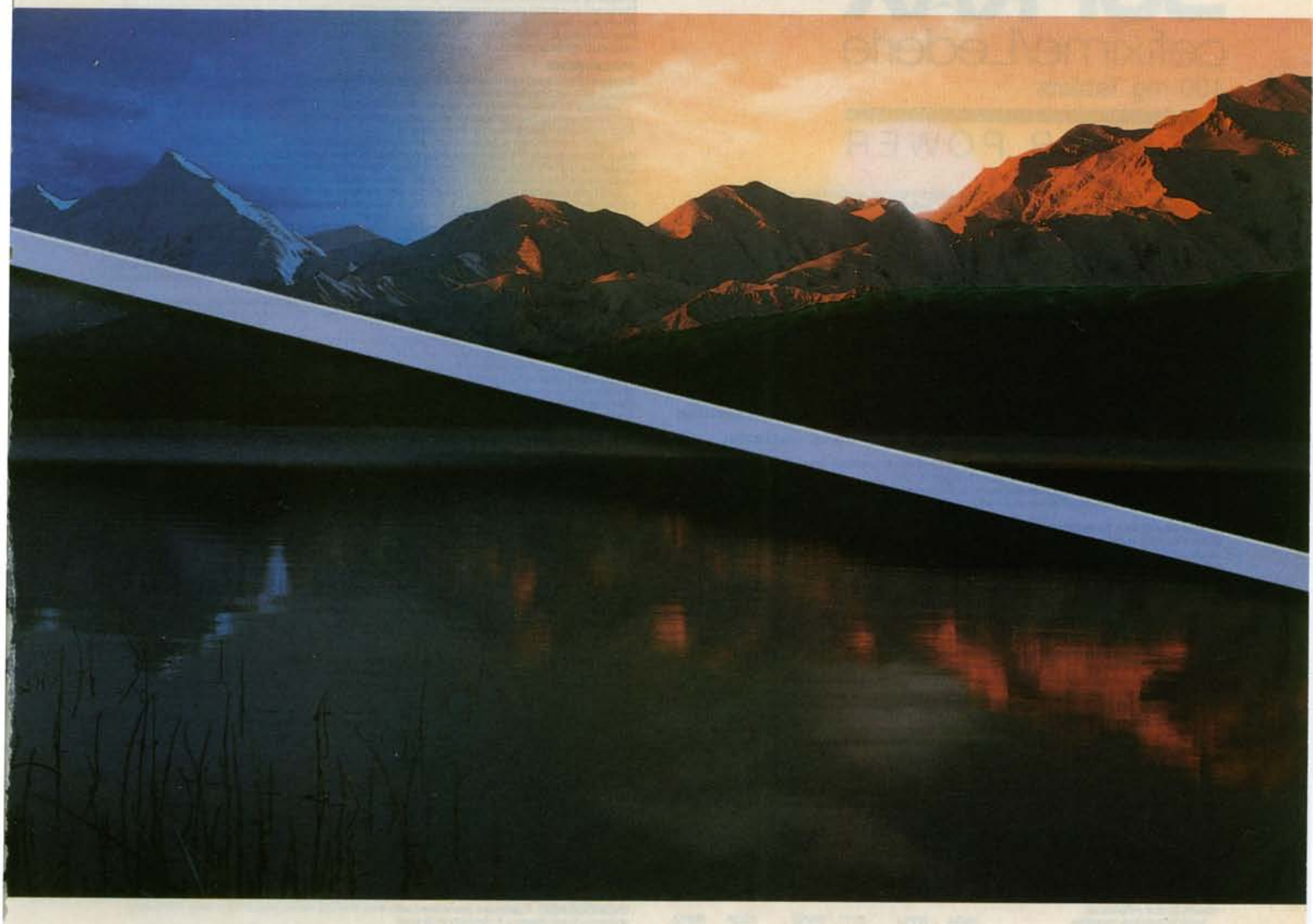
For ß-lactam antibiotics... In order to achieve an optimal antibacterial effect, antibiotic concentrations must exceed the MIC_{90} for the majority of the dosing interval.[1]

*Although a useful guide, *in vitro* activity does not necessarily correlate with clinical response.



aMIC$_{90}$ values from Jones and Barry.[3]

COVERS DAY AND NIGHT



In Bronchitis: Excellent Clinical Results†

- In a surveillance study of over 9600 patients, SUPRAX cured or improved 95% of patients[4†]

Acute Bronchitis	Acute Exacerbations of Chronic Bronchitis
95%	95%
Cured or improved (n=8,127)	Cured or improved (n=1,322)

† Due to indicated susceptible organisms.

ONCE-A-DAY

SUPRAX®

cefixime/Lederle

400 mg Tablets

24 HOUR POWER

SUPRAX is administered as a single dose, once a day, or if preferred, in equally divided doses twice a day.

Please see brief summary of Prescribing Information on adjacent page.

7508-2

ONCE-A-DAY

SUPRAX®

cefixime/Lederle

400 mg Tablets

24 HOUR POWER

References:

1. Ebert SC, Craig WA. Pharmacodynamic properties of antibiotics: application to drug monitoring and dosage regimen design. *Infect Control Hosp Epidemiol.* 1990;11(6):319-326. **2.** Schentag JJ. Phamacokinetic profiles as predictors of therapeutic success. In: *Respiratory Infections: Therapeutic Considerations in a Dynamic Environment.* Lederle Laboratories; 1990. Data on file. Lederle Laboratories, Pearl River, NY. **3.** Jones RN, Barry AL. Antimicrobial activity, spectrum and recommendations for disk diffusion susceptibility testing of ceftibuten (7432-S; SCH 39720), a new orally administered cephalosporin. *Antimicrob Agents Chemother.* 1988;32(10):1576-1582. **4.** Data on file. Lederle Laboratories, Pearl River, NY.

Brief Summary

SUPRAX® cefixime

Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE

Otitis Media caused by *Haemophilus influenzae* (beta-lactamase positive and negative strains), *Moraxella (Branhamella) catarrhalis* (most of which are beta-lactamase positive), and *Streptococcus pyogenes.**

Note: For information on otitis media caused by *Streptococcus pneumoniae*, see **CLINICAL STUDIES** section.

Acute Bronchitis and Acute Exacerbations of Chronic Bronchitis caused by *S pneumoniae* and *H influenzae* (beta-lactamase positive and negative strains).

Perform culture and susceptibility studies to determine causative organism and its susceptibility to SUPRAX. Therapy may begin while waiting for study results and may be adjusted when results are known.

Pharyngitis and Tonsillitis caused by *S pyogenes*.

Note: Penicillin is the usual drug of choice in the treatment of *S pyogenes* infections, including the prophylaxis of rheumatic fever. SUPRAX is generally effective in the eradication of *S pyogenes* from the nasopharynx; however, data establishing the efficacy of SUPRAX in the subsequent prevention of rheumatic fever are not available.

Uncomplicated Urinary Tract Infections caused by *Escherichia coli* and *Proteus mirabilis*.

*Efficacy for this organism was studied in fewer than ten patients with otitis media.

CLINICAL STUDIES

In clinical trials of otitis media in nearly 400 children between the ages of 6 months and 10 years, *S pneumoniae* was isolated from 47% of the patients, *H influenzae* from 34%, *B catarrhalis* from 15%, and *S pyogenes* from 4%.

The overall response rate of *S pneumoniae* to cefixime was approximately 10% lower and that of *H influenzae* or *B catarrhalis* approximately 7% higher (12% when beta-lactamase positive strains of *H influenzae* are included) than the response rates of these organisms to the active control drugs.

In these studies, patients were randomized and treated with either cefixime at dose regimens of 4 mg/kg bid or 8 mg/kg qd, or with a standard antibiotic regimen. Sixty-nine to 70% of the patients in each group had resolution of signs and symptoms of otitis media when evaluated 2 to 4 weeks posttreatment, but persistent effusion was found in 15% of the patients. When evaluated at the completion of therapy, 17% of patients receiving cefixime and 14% of patients receiving effective comparative drugs (18% including those patients who had *H influenzae* resistant to the control drug and who received the control antibiotic) were considered to be treatment failures. By the 2- to 4-week follow-up, a total of 30% to 31% of patients had evidence of either treatment failure or recurrent disease.

Bacteriological Outcome of Otitis Media at 2- to 4-Weeks Posttherapy
Based on Repeat Middle Ear Fluid Culture or Extrapolation From Clinical Outcome

Organism	Cefixime(a) 4 mg/kg bid		Cefixime(a) 8 mg/kg qd		Control(a) drugs	
Streptococcus pneumoniae	48/70	(69%)	18/22	(82%)	82/100	(82%)
Haemophilus influenzae beta-lactamase negative	24/34	(71%)	13/17	(76%)	23/34	(68%)
Haemophilus influenzae beta-lactamase positive	17/22	(77%)	9/12	(75%)	1/1(b)	
Moraxella (Branhamella) catarrhalis	26/31	(84%)	5/5		18/24	(75%)
Streptococcus pyogenes	5/5		3/3		6/7	
All Isolates	120/162	(74%)	48/59	(81%)	130/166	(78%)

(a) Number eradicated/number isolated.

(b) An additional 20 beta-lactamase positive strains of *H influenzae* were isolated, but were excluded from this analysis because they were resistant to the control antibiotic. In 19 of these the clinical course could be assessed, and a favorable outcome occurred in 10. When these cases are included in the overall bacteriological evaluation of therapy with the control drugs, 140/185 (76%) of pathogens were considered to be eradicated.

Tablets should not be substituted for suspension when treating otitis media.

CONTRAINDICATIONS

Known allergy to cephalosporins.

WARNINGS

BEFORE THERAPY WITH SUPRAX IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO SUPRAX OCCURS, DISCONTINUE THE DRUG. SERIOUS, ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Administer cautiously to allergic patients.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of severe antibiotic-associated diarrhea including pseudomembranous colitis. Pseudomembranous colitis has been reported with the use of SUPRAX and other broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins). It is important to consider this diagnosis in patients who develop diarrhea in association with antibiotic use.

Symptoms of pseudomembranous colitis may occur during or after antibiotic treatment and may range in severity from mild to life threatening. Mild cases usually respond to drug discontinuation alone. Moderate-to-severe cases should be managed with fluid, electrolyte, and protein supplementation. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes of colitis should be excluded.

PRECAUTIONS

General: Prolonged use may result in overgrowth of nonsusceptible organisms. If superinfection occurs, take appropriate measures.

Carefully monitor patients on dialysis. Adjust dosage of SUPRAX in patients with renal impairment and those undergoing continuous ambulatory peritoneal dialysis and hemodialysis. (See **DOSAGE AND ADMINISTRATION** in package insert.)

Prescribe cautiously in patients with a history of gastrointestinal disease, particularly colitis.

Drug Interactions: No significant drug interactions have been reported to date.

Drug/Laboratory Test Interactions: A false-positive reaction for ketones in the urine may occur with tests using nitroprusside but not with those using nitroferricyanide.

SUPRAX administration may result in a false-positive reaction for glucose in the urine using Clinitest®,** Benedict's solution, or Fehling's solution. Use glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix®** or Tes-Tape®**).

A false-positive direct Coombs test has been reported during treatment with other cephalosporin antibiotics; therefore, it should be recognized that a positive Coombs test may be due to the drug.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although no lifetime animal studies have been conducted to evaluate carcinogenic potential, no mutagenic potential of SUPRAX was found in standard laboratory tests. Reproductive studies revealed no fertility impairment in rats at doses up to 125 times the adult therapeutic dose.

Usage in Pregnancy: *Pregnancy Category B:* Reproduction studies have been performed in mice and rats at doses up to 400 times the human dose and have revealed no evidence of harm to the fetus due to SUPRAX.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: SUPRAX has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

Nursing Mothers: It is not known whether SUPRAX is excreted in human milk. Consider discontinuing nursing temporarily during treatment with this drug.

Pediatric Use: Safety and effectiveness of SUPRAX in children aged less than 6 months have not been established.

The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension, was comparable to adult patients receiving tablets.

ADVERSE REACTIONS

Most adverse reactions observed in clinical trials were of a mild and transient nature. Less than four percent (3.8%) of patients in the US trials discontinued therapy because of drug-related adverse reactions. Commonly seen adverse reactions in US trials of the tablet formulation were gastrointestinal events, which were reported in 30% of adult patients on either the bid or the qd regimen. Clinically mild gastrointestinal side effects occurred in 20% of all patients, moderate events occurred in 9% of all patients, and severe adverse reactions occurred in 2% of all patients. Individual event rates included diarrhea 16%, loose or frequent stools 6%, abdominal pain 3%, nausea 7%, dyspepsia 3%, and flatulence 3%. The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension was comparable to adult patients receiving tablets.

Symptoms usually responded to symptomatic therapy or ceased when SUPRAX was discontinued.

Several patients developed severe diarrhea and/or documented pseudomembranous colitis, and a few required hospitalization.

The following adverse reactions have been reported following the use of SUPRAX. Incidence rates were less than 1 in 50 (less than 2%), except as noted above for gastrointestinal events.

Gastrointestinal: Diarrhea, loose stools, abdominal pain, dyspepsia, nausea, and vomiting. Several cases of documented pseudomembranous colitis were identified during the studies. The onset of pseudomembranous colitis symptoms may occur during or after therapy.

Hypersensitivity Reactions: Skin rashes, urticaria, drug fever, and pruritus. Erythema multiforme, Stevens-Johnson syndrome, and serum sickness have been reported rarely.

Hepatic: Transient elevations in SGPT, SGOT, and alkaline phosphatase.

Renal: Transient elevations in BUN or creatinine.

Central Nervous System: Headaches 3%; dizziness.

Hemic and Lymphatic Systems: Transient thrombocytopenia, leukopenia, and eosinophilia. Prolongation in prothrombin time was seen rarely.

Other: Genital pruritus, vaginitis, candidiasis.

The following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Adverse Reactions: Allergic reactions including anaphylaxis, toxic epidermal necrolysis, superinfection, renal dysfunction, toxic nephropathy, hepatic dysfunction, including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see **DOSAGE AND ADMINISTRATION** and **OVERDOSAGE**). If seizures associated with drug therapy occur, discontinue drug. Administer anticonvulsant therapy if clinically indicated.

Abnormal Laboratory Tests: Positive direct Coombs test, elevated bilirubin, elevated LDH, pancytopenia, neutropenia, agranulocytosis.

OVERDOSAGE

Gastric lavage may be indicated; otherwise, no specific antidote exists. Cefixime is not removed in significant quantities from the circulation by hemodialysis or peritoneal dialysis. Adverse reactions in small numbers of healthy adult volunteers receiving single doses up to 2 g of SUPRAX did not differ from the profile seen in patients treated at the recommended doses.

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Rev. 5/91
10753-91

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I.V. INJECTION/TABLETS

TENORMIN (atenolol) 25, 50, 100 mg tablets

(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT.)

INDICATIONS AND USAGE: Hypertension: TENORMIN is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

Angina Pectoris Due to Coronary Atherosclerosis: TENORMIN is indicated for the long-term management of patients with angina pectoris.

Acute Myocardial Infarction: TENORMIN is indicated in the management of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment can be initiated as soon as the patient's clinical condition allows. (See DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS.) In general, there is no basis for treating patients like those who were excluded from the ISIS-1 trial (blood pressure less than 100 mm Hg systolic, heart rate less than 50 bpm) or have other reasons to avoid beta blockade. As noted above, some subgroups (eg, elderly patients with systolic blood pressure below 120 mm Hg) seemed less likely to benefit.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure. (See WARNINGS.)

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In patients who have congestive heart failure controlled by digitalis and/or diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In patients with acute myocardial infarction, cardiac failure which is not promptly and effectively controlled by 80 mg of intravenous furosemide or equivalent therapy is a contraindication to beta-blocker treatment.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues despite adequate digitalization and diuresis, TENORMIN should be withdrawn. (See DOSAGE AND ADMINISTRATION.)

Cessation of Therapy with TENORMIN: Patients with coronary artery disease, who are being treated with TENORMIN, should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in angina patients following the abrupt discontinuation of therapy with beta blockers. The last two complications may occur with or without preceding exacerbation of the angina pectoris. As with other beta blockers, when discontinuation of TENORMIN is planned, the patients should be carefully observed and advised to limit physical activity to a minimum. If the angina worsens or acute coronary insufficiency develops, it is recommended that TENORMIN be promptly reinstituted, at least temporarily. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TENORMIN therapy abruptly even in patients treated only for hypertension. (See DOSAGE AND ADMINISTRATION.)

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta, selectivity is not absolute, the lowest possible dose of TENORMIN should be used with therapy initiated at 50 mg and a beta,-stimulating agent (bronchodilator) should be made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: It is not advisable to withdraw beta-adrenoreceptor blocking drugs prior to surgery in the majority of patients. However, care should be taken when using anesthetic agents such as those which may depress the myocardium. Vagal dominance, if it occurs, may be corrected with atropine (1-2 mg IV).

Additionally, caution should be used when TENORMIN I.V. Injection is administered concomitantly with such agents.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents: eg, dobutamine or isoproterenol with caution (see section on OVERDOSAGE).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. At recommended doses TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Patients suspected of having thyroid disease should be monitored closely when administering TENORMIN I.V. Injection. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely. (See DOSAGE AND ADMINISTRATION.)

Pregnancy and Fetal Injury: TENORMIN can cause fetal harm when administered to a pregnant woman. TENORMIN crosses the placental barrier and appears in cord blood. No studies have been performed on the use of TENORMIN in the first trimester and the possibility of fetal injury cannot be excluded. TENORMIN has been used under close supervision for the treatment of hypertension in the third trimester. Administration of TENORMIN for longer periods to pregnant women in the management of mild to moderate hypertension has been associated with intrauterine growth retardation. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg/day or 25 or more times the maximum recommended human antihypertensive dose.* Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg/day or 12.5 times the maximum recommended human antihypertensive dose.*

*Based on the maximum dose of 100 mg/day in a 50 kg patient.

PRECAUTIONS: General: Patients already on a beta blocker must be evaluated carefully before TENORMIN is administered. Initial and subsequent TENORMIN dosages can be adjusted downward depending on clinical observations including pulse and blood pressure. TENORMIN may aggravate peripheral arterial circulatory disorders.

Impaired Renal Function: The drug should be used with caution in patients with impaired renal function. (SEE DOSAGE AND ADMINISTRATION.)

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Beta blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are coadministered, the beta blocker should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta blockers should be delayed for several days after clonidine administration has stopped.

Caution should be exercised with TENORMIN I.V. Injection when given in close proximity with drugs that may also have a depressant effect on myocardial contractility. On rare occasions, concomitant use of intravenous beta blockers and intravenous verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure, or recent myocardial infarction.

Information on concurrent usage of atenolol and aspirin is limited. Data from several studies, ie, TIMI-II, ISIS-2, currently do not suggest any clinical interaction between aspirin and beta blockers in the acute myocardial infarction setting.

While taking beta blockers, patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat the allergic reaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human antihypertensive dose,* did not indicate a carcinogenic potential of atenolol. A third (24 month) rat study, employing doses of 500 and 1,500 mg/kg/day (250 and 750 times the maximum recommended human antihypertensive dose*) resulted in increased incidences of benign adrenal medullary tumors in males and females, mammary fibroadenomas in females, and anterior pituitary adenomas and thyroid parafollicular cell carcinomas in males. No evidence of a mutagenic potential of atenolol was uncovered in the dominant lethal test (mouse), in vivo cytogenetics test (Chinese hamster), or Ames test (*S typhimurium*).

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose*) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies employing oral atenolol performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human antihypertensive dose*) and increased incidence of atrial degeneration of hearts of male rats at 300 but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human antihypertensive dose,* respectively).

Usage in Pregnancy: Pregnancy Category D: See WARNINGS - Pregnancy and Fetal Injury.

Nursing Mothers: Atenolol is excreted in human breast milk at a ratio of 1.5 to 6.8 when compared to the concentration in plasma. Caution should be exercised when TENORMIN is administered to a nursing woman. Clinically significant bradycardia has been reported in breast fed infants. Premature infants, or infants with impaired renal function, may be more likely to develop adverse effects.

Pediatric Use: Safety and effectiveness in children have not been established.

*Based on the maximum dose of 100 mg/day in 50 kg patient.

ADVERSE REACTIONS: Most adverse effects have been mild and transient.

The frequency estimates in the following table were derived from controlled studies in hypertensive patients in which adverse reactions were either volunteered by the patient (US studies) or elicited, eg, by checklist (foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects of TENORMIN and placebo is similar, causal relationship to TENORMIN is uncertain.

	Volunteered (US Studies)		Total - Volunteered and Elicited (Foreign + US Studies)	
	Atenolol (n = 164) %	Placebo (n = 206) %	Atenolol (n = 399) %	Placebo (n = 407) %
CARDIOVASCULAR				
Bradycardia	3	0	3	0
Cold Extremities	0	0.5	12	5
Postural Hypotension	2	1	4	5
Leg Pain	0	0.5	3	1
CENTRAL NERVOUS SYSTEM/ NEUROMUSCULAR				
Dizziness	4	1	13	6
Vertigo	2	0.5	2	0.2
Light-headedness	1	0	3	0.7
Tiredness	0.6	0.5	26	13
Fatigue	3	1	6	5
Lethargy	1	0	3	0.7
Drowsiness	0.6	0	2	0.5
Depression	0.6	0.5	12	9
Dreaming	0	0	3	1
GASTROINTESTINAL				
Diarrhea	2	0	3	2
Nausea	4	1	3	1
RESPIRATORY (see WARNINGS)				
Wheeziness	0	0	3	3
Dyspnea	0.6	1	6	4

Acute Myocardial Infarction: In a series of investigations in the treatment of acute myocardial infarction, bradycardia and hypotension occurred more commonly, as expected for any beta blocker, in atenolol-treated patients than in control patients. However, these usually responded to atropine and/or to withholding further dosage of atenolol. The incidence of heart failure was not increased by atenolol. Inotropic agents were infrequently used. The reported frequency of these and other events occurring during these investigations is given in the following table.

TENORMIN* (atenolol) 25, 50, 100 mg tablets

In a study of 477 patients, the following adverse events were reported during either intravenous and/or oral atenolol administration:

	Conventional Therapy Plus Atenolol (n=244)		Conventional Therapy Alone (n=233)	
Bradycardia	43	(18%)	24	(10%)
Hypotension	60	(25%)	34	(15%)
Bronchospasm	3	(1.2%)	2	(0.9%)
Heart Failure	46	(19%)	56	(24%)
Heart Block BBB + Major	11	(4.5%)	10	(4.3%)
Axis Deviation	16	(6.6%)	28	(12%)
Supraventricular Tachycardia	28	(11.5%)	45	(19%)
Atrial Fibrillation	12	(5%)	29	(11%)
Atrial Flutter	4	(1.6%)	7	(3%)
Ventricular Tachycardia	39	(16%)	52	(22%)
Cardiac Reinfarction	0	(0%)	6	(2.6%)
Total Cardiac Arrests	4	(1.6%)	16	(6.9%)
Nontatal Cardiac Arrests	4	(1.6%)	12	(5.1%)
Deaths	7	(2.9%)	16	(6.9%)
Cardiogenic Shock	1	(0.4%)	4	(1.7%)
Development of Ventricular Septal Defect	0	(0%)	2	(0.9%)
Development of Mitral Regurgitation	0	(0%)	2	(0.9%)
Renal Failure	1	(0.4%)	0	(0%)
Pulmonary Emboli	3	(1.2%)	0	(0%)

In the subsequent International Study of Infarct Survival (ISIS-1) including over 16,000 patients of whom 8,037 were randomized to receive TENORMIN treatment, the dosage of intravenous and subsequent oral TENORMIN was either discontinued or reduced for the following reasons:

Reasons for Reduced Dosage	IV Atenolol Reduced Dose (< 5mg)*		Oral Partial Dose	
Hypotension/Bradycardia	105	(1.3%)	1168	(14.5%)
Cardiogenic Shock	4	(.04%)	35	(.44%)
Reinfarction	0	(0%)	5	(.06%)
Cardiac Arrest	5	(.06%)	28	(.34%)
Heart Block (> first degree)	5	(.06%)	143	(1.7%)
Cardiac Failure	1	(.01%)	233	(2.9%)
Arrhythmias	3	(.04%)	22	(.27%)
Bronchospasm	1	(.01%)	50	(.62%)

*Full dosage was 10 mg and some patients received less than 10 mg but more than 5 mg.

During postmarketing experience with TENORMIN, the following have been reported in temporal relationship to the use of the drug: elevated liver enzymes and/or bilirubin, headache, impotence, Peyronie's disease, psoriasiform rash or exacerbation of psoriasis, purpura, reversible alopecia, and thrombocytopenia. TENORMIN, like other beta blockers, has been associated with the development of antinuclear antibodies (ANA) and lupus syndrome.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN.

Hematologic: Agranulocytosis.

Allergic: Fever, combined with aching and sore throat, laryngospasm, and respiratory distress.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation of time and place; short-term memory loss; emotional lability with slightly clouded sensorium; and, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Erythematous rash, Raynaud's phenomenon.

Miscellaneous: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small, and in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy. (SEE DOSAGE AND ADMINISTRATION.)

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: Overdosage with TENORMIN has been reported with patients surviving acute doses as high as 5 g. One death was reported in a man who may have taken as much as 10 g acutely.

The predominant symptoms reported following TENORMIN overdose are lethargy, disorder of respiratory drive, wheezing, sinus pause, and bradycardia. Additionally, common effects associated with overdosage of any beta-adrenergic blocking agent and which might also be expected in TENORMIN overdose are congestive heart failure, hypotension, bronchospasm, and/or hypoglycemia.

Treatment of overdose should be directed to the removal of any unabsorbed drug by induced emesis, gastric lavage, or administration of activated charcoal. TENORMIN can be removed from the general circulation by hemodialysis. Other treatment modalities should be employed at the physician's discretion and may include:

BRADYCARDIA: Atropine intravenously. If there is no response to vagal blockade, give isoproterenol cautiously. In refractory cases, a transvenous cardiac pacemaker may be indicated.

HEART BLOCK (SECOND OR THIRD DEGREE): Isoproterenol or transvenous cardiac pacemaker.

CARDIAC FAILURE: Digitalize the patient and administer a diuretic. Glucagon has been reported to be useful.

HYPOTENSION: Vasopressors such as dopamine or norepinephrine (levarterenol). Monitor blood pressure continuously.

BRONCHOSPASM: A beta, stimulant such as isoproterenol or terbutaline and/or aminophylline.

HYPOGLYCEMIA: Intravenous glucose.

Based on the severity of symptoms, management may require intensive support care and facilities for applying cardiac and respiratory support.

DOSAGE AND ADMINISTRATION: Hypertension: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Angina Pectoris: The initial dose of TENORMIN is 50 mg given as one tablet a day. If an optimal response is not achieved within one week, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Some patients may require a dosage of 200 mg once a day for optimal effect.

Twenty-four hour control with once daily dosing is achieved by giving doses larger than necessary to achieve an immediate maximum effect. The maximum early effect on exercise tolerance occurs with doses of 50 to 100 mg, but at these doses the effect at 24 hours is attenuated, averaging about 50% to 75% of that observed with once a day oral doses of 200 mg.

Acute Myocardial Infarction: In patients with definite or suspected acute myocardial infarction, treatment with TENORMIN I.V. Injection should be initiated as soon as possible after the patient's arrival in the hospital and after eligibility is established. Such treatment should be initiated in a coronary care or similar unit immediately after the patient's hemodynamic condition has stabilized. Treatment should begin with the intravenous administration of 5 mg TENORMIN over 5 minutes followed by another 5 mg intravenous injection 10 minutes later. TENORMIN I.V. Injection should be administered under carefully controlled conditions including monitoring of blood pressure, heart rate, and electrocardiogram. Dilutions of TENORMIN I.V. Injection in Dextrose Injection USP, Sodium Chloride Injection USP, or Sodium Chloride and Dextrose Injection may be used. These admixtures are stable for 48 hours if they are not used immediately.

In patients who tolerate the full intravenous dose (10 mg), TENORMIN Tablets 50 mg should be initiated 10 minutes after the last intravenous dose followed by another 50 mg oral dose 12 hours later. Thereafter, TENORMIN can be given orally either 100 mg once daily or 50 mg twice a day for a further 6-9 days or until discharge from the hospital. If bradycardia or hypotension requiring treatment or any other untoward effects occur, TENORMIN should be discontinued.

Data from other beta blocker trials suggest that if there is any question concerning the use of IV beta blocker or clinical estimate that there is a contraindication, the IV beta blocker may be eliminated and patients fulfilling the safety criteria may be given TENORMIN Tablets 50 mg twice daily or 100 mg once a day for at least seven days (if the IV dosing is excluded).

Although the demonstration of efficacy of TENORMIN is based entirely on data from the first seven postinfarction days, data from other beta blocker trials suggest that treatment with beta blockers that are effective in the postinfarction setting may be continued for one to three years if there are no contraindications.

TENORMIN is an additional treatment to standard coronary care unit therapy.

Elderly Patients or Patients with Renal Impairment: TENORMIN is excreted by the kidneys; consequently dosage should be adjusted in cases of severe impairment of renal function. Some reduction in dosage may also be appropriate for the elderly, since decreased kidney function is a physiologic consequence of aging. Atenolol excretion would be expected to decrease with advancing age.

No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 mL/min/1.73m². Accumulation of atenolol and prolongation of its half-life were studied in subjects with creatinine clearance between 5 and 105 mL/min. Peak plasma levels were significantly increased in subjects with creatinine clearances below 30 mL/min.

The following maximum oral dosages are recommended for elderly, renally-impaired patients and for patients with renal impairment due to other causes:

Creatinine Clearance (mL/min/1.73m²)	Atenolol Elimination Half-Life (h)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	25 mg daily

Some renally-impaired or elderly patients being treated for hypertension may require a lower starting dose of TENORMIN: 25 mg given as one tablet a day. If this 25 mg dose is used, assessment of efficacy must be made carefully. This should include measurement of blood pressure just prior to the next dose ("trough" blood pressure) to ensure that the treatment effect is present for a full 24 hours.

Although a similar dosage reduction may be considered for elderly and/or renally-impaired patients being treated for indications other than hypertension, data are not available for these patient populations.

Patients on hemodialysis should be given 25 mg or 50 mg after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

Cessation of Therapy in Patients with Angina Pectoris: If withdrawal of TENORMIN therapy is planned, it should be achieved gradually and patients should be carefully observed and advised to limit physical activity to a minimum.

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

HOW SUPPLIED

TENORMIN Tablets: Tablets of 25 mg atenolol, NDC 0310-0107 (round, flat, uncoated white tablets with "T" debossed on one side and 107 debossed on the other side) are supplied in bottles of 100 tablets.

Tablets of 50 mg atenolol, NDC 0310-0105 (round, flat, uncoated white tablets identified with ICI debossed on one side and 105 debossed on the other side, bisected) are supplied in bottles of 100 tablets and 1000 tablets, and unit dose packages of 100 tablets. These tablets are distributed by ICI Pharma.

Tablets of 100 mg atenolol, NDC 0310-0101 (round, flat, uncoated white tablets with ICI debossed on one side and 101 debossed on the other side) are supplied in bottles of 100 tablets and unit dose packages of 100 tablets. These tablets are distributed by ICI Pharma.

Store at controlled room temperature, 15°-30 °C (59°-86 °F). Dispense in well-closed, light resistant containers.

TENORMIN I.V. Injection

TENORMIN I.V. Injection, NDC 0310-0108, is supplied as 5 mg atenolol in 10 mL ampules of isotonic citrate-buffered aqueous solution.

Protect from light. Keep ampules in outer packaging until time of use. Store at room temperature.

REV Y 03/92

ICI Pharma

A business unit of ICI Americas Inc.
Wilmington, Delaware 19897 USA

FSA-1511 1192 ICI-2870

WHY CONSIDER TENORMIN BEFORE ALL OTHER BETA BLOCKERS?

- **Convenient, once-daily dosing for all indications**
- **Effective control of blood pressure and angina**
- **Cardioprotection—improving survival during and after MI[1,2]***
- **Well-tolerated**

I.V. INJECTION/TABLETS

TENORMIN®
(atenolol)

* Good clinical judgment suggests that patients who are dependent on sympathetic stimulation for adequate cardiac output and BP are not good candidates for beta blockade. In addition to patients excluded from the ISIS-1 study, those with borderline BP (ie, systolic < 120, especially if over age 60) are less likely to benefit.

References: 1. ISIS-1 (First International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. *Lancet.* 1986;2:57-66. **2.** Glamann DB, Lange RA, Hillis LD. Beneficial effect of long-term beta blockade after acute myocardial infarction in patients without anterograde flow in the infarct artery. *Am J Cardiol.* 1991;68:150-154.

See adjacent page for brief summary of prescribing information.

Announcing

The American Medical Association

Morris Fishbein Fellowship

July 1, 1993 through
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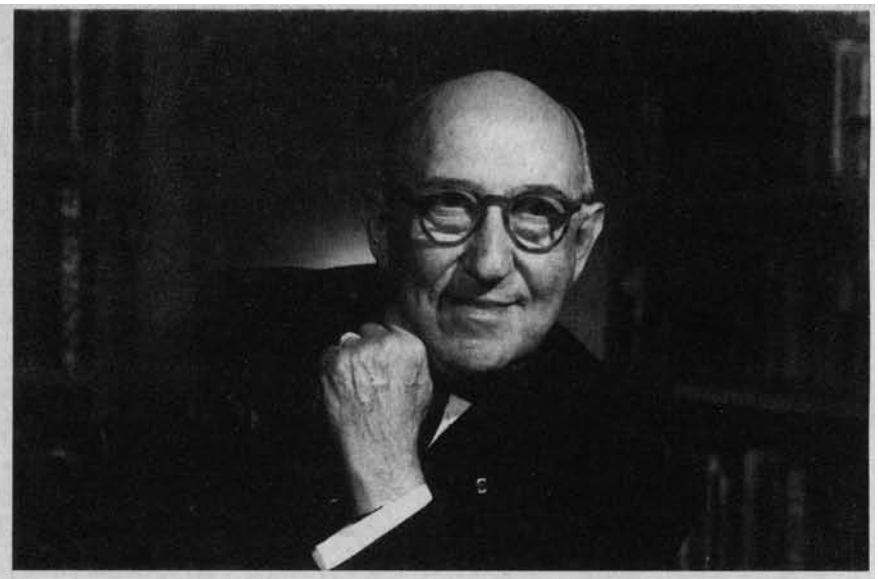


Applications are now being taken for the Morris Fishbein Fellowship in Medical Journalism sponsored by the American Medical Association. Physicians interested in making a substantial commitment to medical journalism are invited to apply for this full-time one-year fellowship program.

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 all aspects of manuscript 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, Journal of the American Medical Association, 515 North State Street, Chicago, IL 60610.

Deadline For Applying Completed applications should be forwarded as soon as possible and must be received no later than March 1, 1993

American Medical Association

Physicians dedicated to the health of America

NEW FOR ANGINA

THE ONE

CARDIZEM® CD

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

ONCE A DAY

NEW FOR ANGINA

CARDIZEM® CD

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

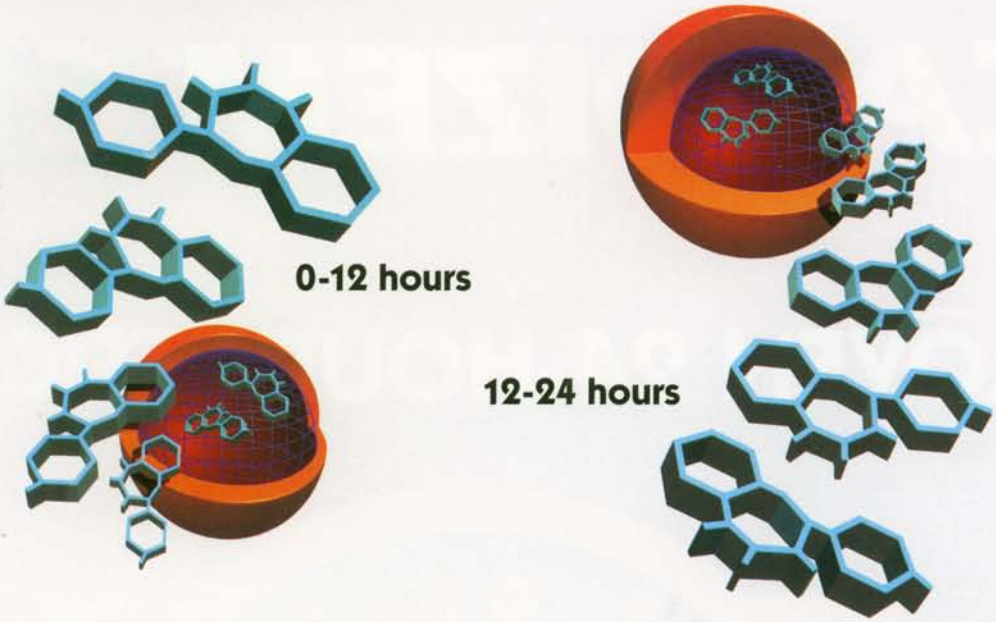
PROVEN 24-HOUR CONTROL

CCDAK514/A7856

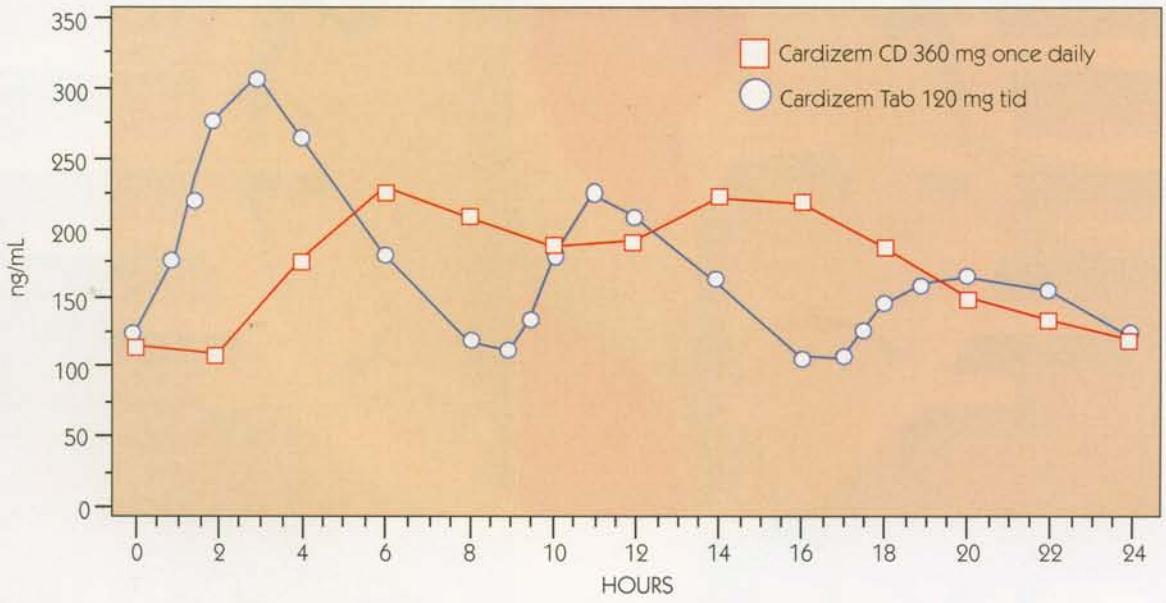
0119A3

IN ANGINA AND HYPERTENSION*

24-hour control through a unique delivery system designed specifically for diltiazem†



CARDIZEM CD provides 24-hour plasma levels similar to those of Cardizem tablets tid at steady state[1]



One daily dose provides effective plasma levels[1]

* Cardizem CD is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive medications. Cardizem CD is indicated for the management of chronic stable angina and angina due to coronary artery spasm.

† Patent pending.

Please see brief summary of prescribing information on adjacent page.

NEW FOR ANGINA

CARDIZEM® CD

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

PROVEN 24-HOUR EFFICACY

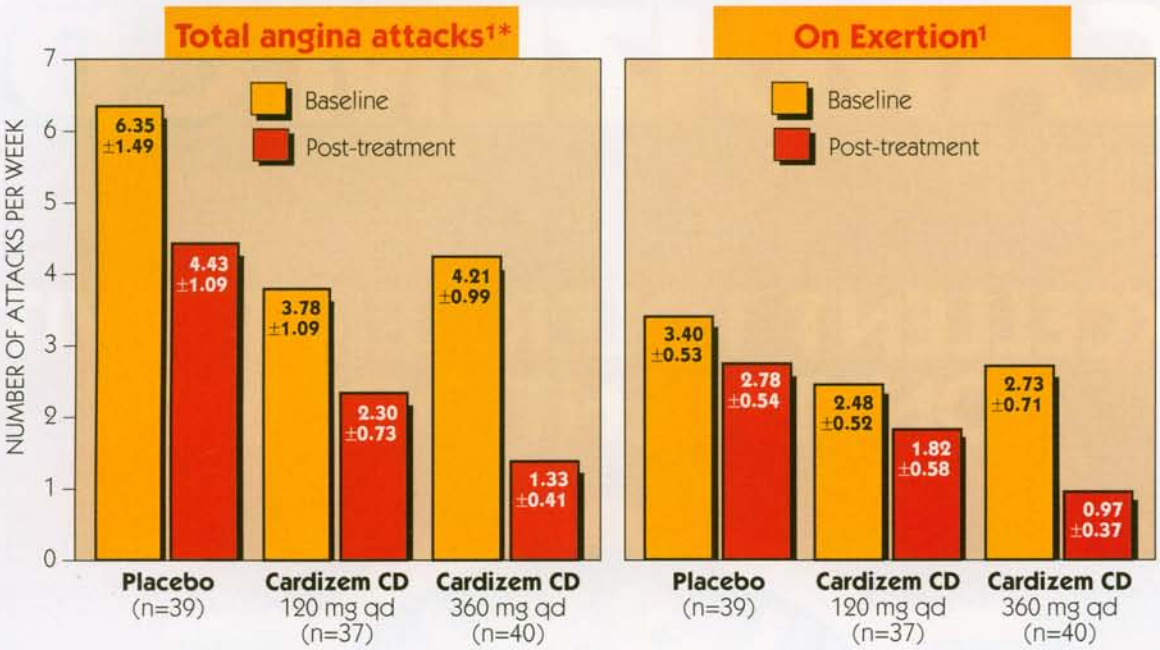
ONCE A DAY

CCDAK514/A7856

0119A3

IN ANGINA

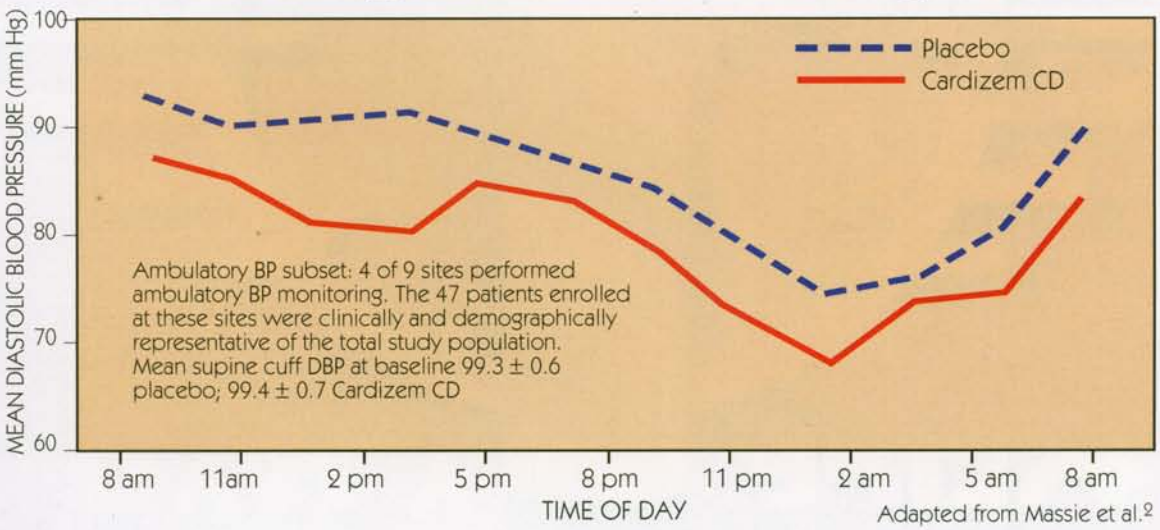
Reduces the frequency of angina attacks —through 24 hours[1]



* At rest and on exertion.

IN HYPERTENSION

Consistent antihypertensive effect seen throughout 24 hours[2]



Adapted from Massie et al.[2]

- Overall study results (127 patients) show a significant mean change at 24 hours in both diastolic (P=0.0075) and systolic (P=0.0009) blood pressure vs placebo[2]
- Cardizem CD average daily dose 268 mg/day

Unlike some once-a-day antihypertensives, titration to bid dosing is not necessary with Cardizem CD

Please see brief summary of prescribing information on adjacent page.

NEW FOR ANGINA

CARDIZEM® CD

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

EXCELLENT TOLERABILITY WITH CONVENIENT DOSING

CCDAK514/A7856

0119A3

IN ANGINA AND HYPERTENSION

Extremely well tolerated[3]

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

In clinical trials of Cardizem CD capsules, Cardizem tablets, and Cardizem SR capsules involving over 3200 patients, the most common events (ie, greater than 1%) were edema (4.6%), headache (4.6%), dizziness (3.5%), asthenia (2.6%), first-degree AV block (2.4%), bradycardia (1.7%), flushing (1.4%), nausea (1.4%), and rash (1.2%).

COMPLIANCE-ENHANCING ONCE-DAILY DOSING

120-mg capsules **180-mg capsules** **240-mg capsules** **300-mg capsules**

For angina or hypertensive patients, a recommended starting dose:

- **One 180-mg capsule daily**
- **If necessary, titrate to optimum response**

LOWER PRICE

Based on average wholesale prices using equivalent mg/day doses[4]:

- **35% lower cost than Cardizem® (diltiazem HCl) tablets for angina**
  — Cardizem tablets are available as 30, 60, 90, and 120 mg
- **25% lower cost than Cardizem® SR (diltiazem HCl) capsules for hypertension**
  — Cardizem SR capsules are available as 60, 90, and 120 mg

Please see brief summary of prescribing information on adjacent page.

ONCE-A-DAY CARDIZEM® CD

(diltiazem HCl)

24-HOUR CONTROL OF ANGINA AND HYPERTENSION

Brief Summary of
Prescribing Information as of October 1992 (2)
CARDIZEM® CD
(diltiazem hydrochloride)
Capsules

Brief Summary of
Prescribing Information as of April 1992
CARDIZEM® SR
(diltiazem hydrochloride)
Sustained Release Capsules

Brief Summary of
Prescribing Information as of January 1991
CARDIZEM®
(diltiazem hydrochloride)
Tablets

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

1. **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 3,290 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.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of CARDIZEM (diltiazem hydrochloride) in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters of renal and hepatic function should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

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

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

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs such as cyclosporin, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM 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%. 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 1,200 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.

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. In domestic placebo-controlled angina trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The adverse events described below represent events observed in clinical studies of hypertensive patients receiving either CARDIZEM Tablets or CARDIZEM SR Capsules as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients taking CARDIZEM Tablets or CARDIZEM SR Capsules studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and first-degree AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related.

Double Blind Placebo-Controlled Hypertension Trials

Adverse	Diltiazem N = 315 # pts (%)	Placebo N = 211 # pts (%)
Headache	38 (12%)	17 (8%)
AV Block First Degree	24 (7.6%)	4 (1.9%)
Dizziness	22 (7%)	6 (2.8%)
Edema	19 (6%)	2 (0.9%)
Bradycardia	19 (6%)	3 (1.4%)
ECG Abnormality	13 (4.1%)	3 (1.4%)
Asthenia	10 (3.2%)	1 (0.5%)
Constipation	5 (1.6%)	2 (0.9%)
Dyspepsia	4 (1.3%)	1 (0.5%)
Nausea	4 (1.3%)	2 (0.9%)
Palpitations	4 (1.3%)	2 (0.9%)
Polyuria	4 (1.3%)	2 (0.9%)
Somnolence	4 (1.3%)	---
Alk Phos Increase	3 (1%)	1 (0.5%)
Hypotension	3 (1%)	1 (0.5%)
Insomnia	3 (1%)	1 (0.5%)
Rash	3 (1%)	1 (0.5%)
AV Block Second Degree	2 (0.6%)	---

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 Capsules Placebo-Controlled Angina and Hypertension Trials Combined

Adverse Reaction	CARDIZEM CD N = 607	Placebo N = 301
Headache	5.4%	5.0%
Dizziness	3.0%	3.0%
Bradycardia	3.3%	1.3%
AV Block First Degree	3.3%	0.0%
Edema	2.6%	1.3%
ECG Abnormality	1.6%	2.3%
Asthenia	1.8%	1.7%

In clinical trials of CARDIZEM CD Capsules, CARDIZEM Tablets, and CARDIZEM SR Capsules involving over 3200 patients, the most common events (ie, greater than 1%) were edema (4.6%), headache (4.6%), dizziness (3.5%), asthenia (2.6%), first-degree AV block (2.4%), bradycardia (1.7%), flushing (1.4%), nausea (1.4%), and rash (1.2%).

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

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

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

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

Dermatological: Petechiae, photosensitivity, pruritus, urticaria

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular 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.

CARDIZEM® CD
Prescribing Information as of October 1992 (2)

CARDIZEM® SR
Prescribing Information as of April 1992

CARDIZEM®
Prescribing Information as of January 1991

Marion Merrell Dow Inc.
Kansas City, Missouri 64114

cdrtb1092492191a

References: 1. Data on file, Marion Merrell Dow Inc. **2.** Massie BM, Der E, Herman TS, Topolski P, Park GD, Stewart WH. *Clin Cardiol* 1992;15:365-368. **3.** Cardizem CD prescribing information. **4.** *Red Book Update*. 1992;11(10):7.

Available as Once-A-Day


120-mg capsules


180-mg capsules


240-mg capsules


300-mg capsules

℞ *Cardizem CD Start with one 180-mg capsule daily*

MARION MERRELL DOW INC.
PRESCRIPTION PRODUCTS DIVISION
KANSAS CITY, MO 64114

CCDAK514/A7856

0119A3

HARNESS THE TRIPLE
THE POTENT

1. Fungicidal action

- **Naftin® is fungicidal, not just fungistatic, to dermatophytes at low concentrations.***
- **Imidazoles (Spectazole®, Nizoral®, Lotrimin® and Lotrisone®*) are fungistatic at low concentrations.**

3. Broad spectrum coverage

- **Naftin® is effective against the dermatophytes which are associated with the majority of tinea infections.**

Recommend Broad Spectrum Naftin® (naftifine hydro
for the everyday treatment of tinea pedis, tinea crur

The Standard of Skin Care

ALLERGAN Herbert
Skin Care Division Of Allergan, Inc.
Irvine, CA 92715

For a copy of "Diagnosis and Treatment of Fungal Inf

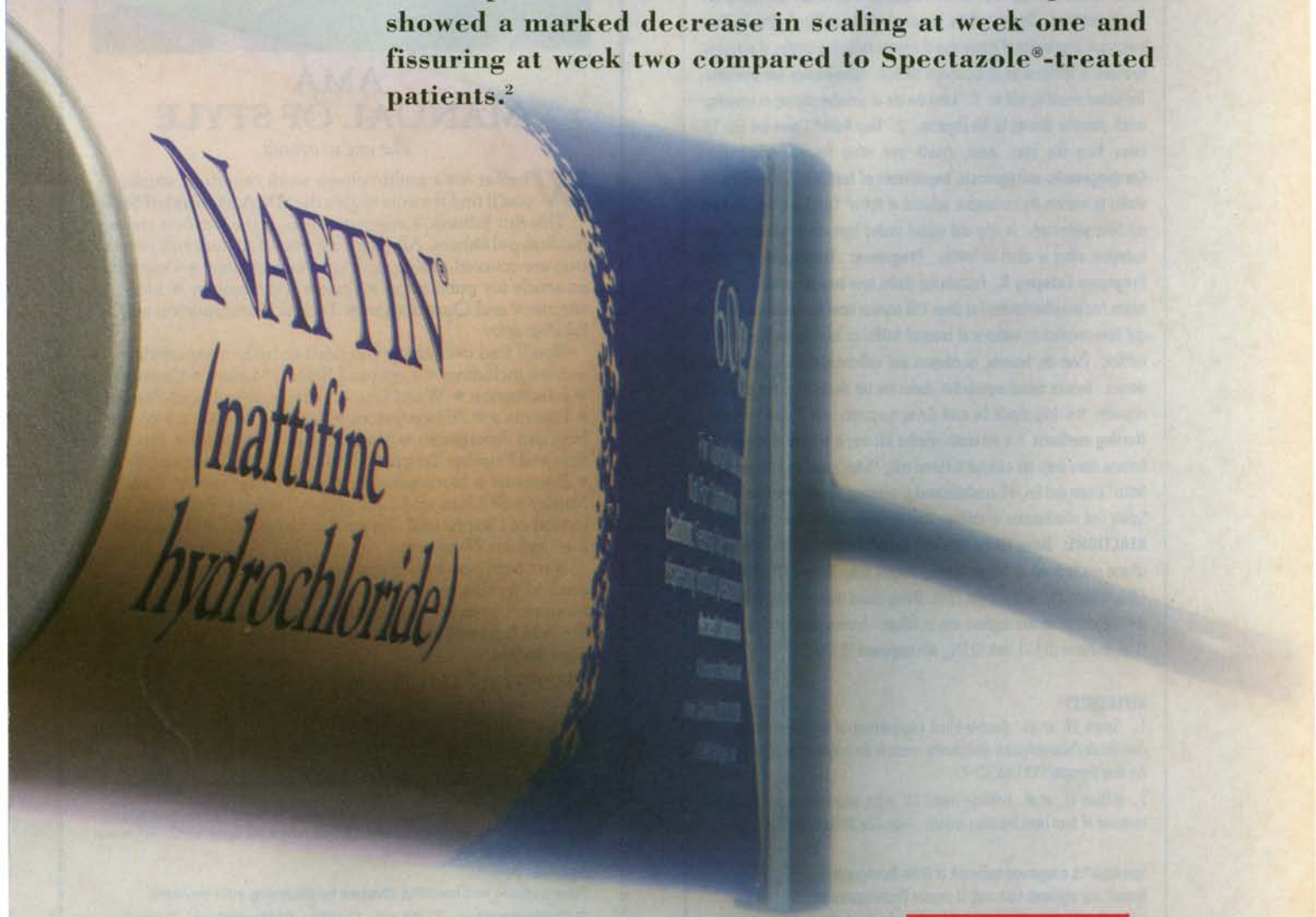
**In vitro data*, clinical significance unknown. A low incidence of irritation and

Please see adjacent page for brief summary of pres

-ACTION POWER OF ANTIFUNGAL.

2. Rapid symptomatic relief

- Even without a steroid, Naftin® Cream is as effective as Lotrisone® at relieving tinea-related pruritus and erythema.[1]
- In comparative studies, Naftin® Cream-treated patients showed a marked decrease in scaling at week one and fissuring at week two compared to Spectazole®-treated patients.[2]



chloride) 1% Cream and Gel
is and tinea corporis.

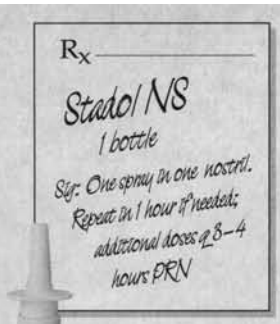
ctions," call: **1-800-934-3169.**

dryness was observed in clinical trials with Naftin® Cream.
cribing information.

NAFTIN®
(naftifine hydrochloride) 1%
Cream 15g, 30g, 60g • Gel 20g, 40g, 60g

STADOL® NS™
(butorphanol tartrate) Nasal Spray

Acute Pain Relief, Delivered in Minutes



Brief Summary

INDICATIONS
STADOL® NS™ (butorphanol tartrate) Nasal Spray is indicated for the management of pain when the use of an opioid analgesic is appropriate.

CONTRAINDICATIONS
STADOL NS is contraindicated in patients hypersensitive to butorphanol tartrate or the preservative benzethonium chloride.

WARNINGS
Patients Dependent on Narcotics
Because of its opioid antagonist properties, butorphanol is not recommended for use in patients dependent on narcotics. Such patients should have an adequate period of withdrawal from opioid drugs prior to beginning butorphanol therapy. In patients taking opioid analgesics chronically, butorphanol has precipitated withdrawal symptoms such as anxiety, agitation, mood changes, hallucinations, dysphoria, weakness and diarrhea.

Because of the difficulty in assessing opioid tolerance in patients who have recently received repeated doses of narcotic analgesic medication, caution should be used in the administration of butorphanol to such patients.

PRECAUTIONS
Head Injury and Increased Intracranial Pressure
As with other opioids, the use of butorphanol in patients with head injury may be associated with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, drug-induced miosis, and alterations in mental state that would obscure the interpretation of the clinical course of patients with head injuries. In such patients, butorphanol should be used only if the benefits of use outweigh the potential risks.

Disorders of Respiratory Function or Control
Butorphanol may produce respiratory depression, especially in patients receiving other CNS active agents, or patients suffering from CNS diseases or respiratory impairment.

Hepatic and Renal Disease
In patients with severe hepatic or renal disease the initial dosage interval for STADOL NS should be increased to 6-8 hours until the response has been well characterized. Subsequent doses should be determined by patient response rather than being scheduled at fixed intervals.

Cardiovascular Effects
Because butorphanol may increase the work of the heart, especially the pulmonary circuit, the use of butorphanol in patients with acute myocardial infarction, ventricular dysfunction, or coronary insufficiency should be limited to those situations where the benefits clearly outweigh the risk.

Severe hypertension has been reported rarely during butorphanol therapy. In such cases, butorphanol should be discontinued and the hypertension treated with antihypertensive drugs. In patients who are not opioid dependent, naloxone has also been reported to be effective.

Drug Interactions
Concurrent use of butorphanol with central nervous system depressants (e.g., alcohol, barbiturates, tranquilizers, and antihistamines) may result in increased central nervous system depressant effects. When used concurrently with such drugs, the dose of butorphanol should be the smallest effective dose and the frequency of dosing reduced as much as possible when administered concomitantly with drugs that potentiate the action of opioids.

It is not known if the effects of butorphanol are altered by concomitant medications that affect hepatic metabolism of drugs (cimetidine, erythromycin, theophylline, etc.), but physicians should be alert to the possibility that a smaller initial dose and longer intervals between doses may be needed.

The fraction of STADOL NS absorbed is unaffected by the concomitant administration of a nasal vasoconstrictor (oxymetazoline), but the rate of absorption is decreased. Therefore, a slower onset can be anticipated if STADOL NS is administered concomitantly with, or immediately following, a nasal vasoconstrictor.

No information is available about the use of butorphanol concurrently with MAO inhibitors.

Use in Ambulatory Patients
Drowsiness and dizziness related to the use of butorphanol may impair mental and/or physical abilities required for the performance of potentially hazardous tasks (e.g., driving, operating machinery, etc.). Patients should be told to use caution in such activities until their individual responses to butorphanol have been well characterized.

Alcohol should not be consumed while using butorphanol. Concurrent use of butorphanol with central nervous system depressants (e.g., alcohol, barbiturates, tranquilizers, and antihistamines) may result in increased central nervous system depressant effects.

Patients should be instructed on the proper use of STADOL NS.

Carcinogenesis, Mutagenesis, Impairment of Fertility
The carcinogenic potential of butorphanol has not been adequately evaluated.

Butorphanol was not genotoxic in *S. typhimurium* or *E. coli* assays or in unscheduled DNA synthesis and repair assays conducted in cultured human fibroblast cells.

Rats treated orally with 160 mg/kg/day (944 mg/sq.m.) had a reduced pregnancy rate. However, a similar effect was not observed with a 2.5 mg/kg/day (14.75 mg/sq.m.) subcutaneous dose.

Pregnancy
Pregnancy Category C

There are no adequate and well-controlled studies of butorphanol in pregnant women before 37 weeks of gestation.

Reproduction studies in mice, rats and rabbits during organogenesis did not reveal any teratogenic potential to butorphanol. Pregnant rats treated subcutaneously with butorphanol at 1 mg/kg (5.9 mg/sq.m.) had a higher frequency of stillbirths than controls. Butorphanol at 30 mg/kg/oral (5.1 mg/sq.m.) and 60 mg/kg/oral (10.2 mg/sq.m.) also showed higher incidences of post implantation loss in rabbits.

Labor and Delivery
STADOL NS is not recommended during labor or delivery because there is no clinical experience with its use in this setting.

Nursing Mothers
Butorphanol has been detected in milk following administration of STADOL Injectable to nursing mothers. The amount an infant would receive is probably clinically insignificant (estimated 4 microgram/liter of milk in a mother receiving 2 mg IM four times a day).

Although there is no clinical experience with the use of STADOL NS in nursing mothers, it should be assumed that butorphanol will appear in the milk in similar amounts following the nasal route of administration.

Pediatric Use
Butorphanol is not recommended for use in patients below 18 years of age because safety and efficacy have not been established in this population.

Geriatric Use
Initially a 1 mg dose of STADOL® NS™ (butorphanol tartrate) Nasal Spray should generally be used in geriatric patients and 90-120 minutes should elapse before deciding whether a second 1 mg dose is needed.

Due to changes in clearance, the mean half-life of butorphanol is increased by 25% (to over 6 hours) in patients over the age of 65. Elderly patients may be more sensitive to its side effects. Results from a long-term clinical safety trial suggest that elderly patients may be less tolerant of dizziness due to STADOL NS than younger patients.

ADVERSE REACTIONS
A total of 2446 patients were studied in butorphanol clinical trials. Approximately half received STADOL Injectable with the remainder receiving STADOL NS. In nearly all cases the type and incidence of side effects with butorphanol by any route were those commonly observed with opioid analgesics.

The adverse experiences described below are based on data from short- and long-term clinical trials in patients receiving butorphanol by any route and from post-marketing experience with STADOL Injectable. There has been no attempt to correct for placebo effect or to subtract the frequencies reported by placebo treated patients in controlled trials.

REACTIONS
The most frequently reported adverse experiences across all clinical trials with STADOL Injectable and STADOL NS were somnolence (43%), dizziness (19%), nausea and/or vomiting (13%). In long-term trials with STADOL NS only, nasal congestion (13%) and insomnia (11%) were frequently reported.

The following adverse experiences were reported at a frequency of 1% or greater, and were considered to be probably related to the use of butorphanol:

BODY AS A WHOLE: asthenia/lethargy*, headache*, sensation of heat

CARDIOVASCULAR: VASODILATION*, PALPITATIONS

DIGESTIVE: ANOREXIA*, CONSTIPATION*, dry mouth*, nausea and/or vomiting (13%), stomach pain

NERVOUS: anxiety, confusion*, dizziness (19%), euphoria, floating feeling, INSOMNIA (11%), nervousness, paresthesia, somnolence (43%), TREMOR

RESPIRATORY: BRONCHITIS, COUGH, DYSPNEA*, EPISTAXIS*, NASAL CONGESTION (13%), NASAL IRRITATION*, PHARYNGITIS*, RHINITIS*, SINUS CONGESTION*, SINUSITIS, UPPER RESPIRATORY INFECTION*

SKIN AND APPENDAGES: sweating/clammy*, pruritus

SPECIAL SENSES: blurred vision, EAR PAIN, TINNITUS*, UNPLEASANT TASTE* (also seen in short-term trials with STADOL NS)

(Reactions occurring with a frequency of 3-9% are marked with an asterisk.* Reactions reported predominantly from long-term trials with STADOL NS are CAPITALIZED.)

The following adverse experiences were reported with a frequency of less than 1%, in clinical trials or from post-marketing experience and were considered to be probably related to the use of butorphanol.

CARDIOVASCULAR: hypotension

NERVOUS: abnormal dreams, agitation, *drug dependence*, dysphoria, hallucinations, hostility

SKIN AND APPENDAGES: rash/hives

UROGENITAL: impaired urination

(Reactions reported only from post-marketing experience are *italicized*.)

The following infrequent additional adverse experiences were reported in a frequency of less than 1% of the patients studied in short-term STADOL NS trials and from post-marketing experiences under circumstances where the association between these events and butorphanol administration is unknown. They are being listed as alerting information for the physician.

BODY AS A WHOLE: edema

CARDIOVASCULAR: hypertension

NERVOUS: *convulsion, delusions*, depression

RESPIRATORY: *apnea*, shallow breathing

(Reactions reported only from post-marketing experience are *italicized*.)

DRUG ABUSE AND DEPENDENCE
Although the mixed agonist-antagonist opioid analgesics, as a class, have lower abuse potential than morphine, all such drugs can be and have been reported to be abused.

Chronic use of STADOL Injectable has been reported to result in mild withdrawal syndromes, and reports of overuse and self-reported addiction have been received.

Among 161 patients who used STADOL NS for 2 months or longer approximately 3% had behavioral symptoms suggestive of possible abuse. Approximately 1% of these patients reported significant overuse. Symptoms such as anxiety, agitation, and diarrhea were observed. Symptoms suggestive of opioid withdrawal occurred in 2 patients who stopped the drug abruptly after using 16 mg a day or more for longer than 3 months.

Special care should be exercised in administering butorphanol to emotionally unstable patients and to those with a history of drug misuse. When long-term therapy is necessary, such patients should be closely supervised.

OVERDOSAGE
Clinical Manifestations
The clinical manifestations of overdose are those of opioid drugs, the most serious of which are hypoventilation, cardiovascular insufficiency and/or coma.

Overdose can occur due to accidental or intentional misuse of butorphanol, especially in young children who may gain access to the drug in the home.

Treatment
The management of suspected butorphanol overdosage includes maintenance of adequate ventilation, peripheral perfusion, normal body temperature, and protection of the airway. Patients should be under continuous observation with adequate serial measures of mental state, responsiveness and vital signs. Oxygen and ventilatory assistance should be available with continual monitoring by pulse oximetry if indicated. In the presence of coma, placement of an artificial airway may be required. An adequate intravenous portal should be maintained to facilitate treatment of hypotension associated with vasodilation.

The use of a specific opioid antagonist such as naloxone should be considered. As the duration of butorphanol action usually exceeds the duration of action of naloxone, repeated dosing with naloxone may be required.

DOSAGE AND ADMINISTRATION
Factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and surgical procedure involved. Use in the elderly, patients with hepatic or renal disease or in labor requires extra caution (see PRECAUTIONS). The following doses are for patients who do not have impaired hepatic or renal function and who are not on CNS active agents.

The usual recommended dose for initial nasal administration is 1 mg (1 spray in **one** nostril). Adherence to this dose reduces the incidence of drowsiness and dizziness. If adequate pain relief is not achieved within 60-90 minutes, an additional 1 mg dose may be given.

The initial two dose sequence outlined above may be repeated in 3-4 hours as needed.

Depending on the severity of the pain, an initial dose of 2 mg (1 spray in **each** nostril) may be used in patients who will be able to remain recumbent in the event drowsiness or dizziness occurs. In such patients single additional 2 mg doses should not be given for 3-4 hours.

Safety and Handling
STADOL NS is an open delivery system with increased risk of exposure to health care workers.

In the priming process, a certain amount of butorphanol may be aerosolized, therefore the pump sprayer should be aimed away from the patient or other people or animals.

The unit should be disposed of by unscrewing the cap, rinsing the bottle, and placing the parts in a waste container.

HOW SUPPLIED
STADOL NS is supplied in a child-resistant prescription vial containing a metered-dose spray pump and protective clip with dust cover, a bottle of nasal spray solution, and a patient instruction leaflet. On average, one bottle will deliver 14-15 doses if no reprimming is necessary.

NDC 0087-5650-41: 10 mg per mL, 2.5-mL bottle.

Storage Conditions
Store below 86°F (30°C). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

CAUTION: Federal law prohibits dispensing without prescription.

Mead Johnson LABORATORIES
A Bristol-Myers Squibb Company
Princeton, New Jersey 08543 U.S.A.

From Mead Johnson Laboratories

Acute pain relief... from a nasal spray

A Potent Analgesic

- Synthetically derived opioid analgesic with sedative properties
- Efficacy comparable to IM meperidine at equipotent doses[1]
- Somnolence (43%) is the most frequently reported side effect*

In a Convenient Nasal Spray

- The only nasal spray analgesic
- Well suited for outpatient management of acute pain with appropriate medical instruction
- Not a federally controlled substance

Effective in Acute Pain

- Demonstrated efficacy in relief of acute pain following invasive surgical procedures[1]
- Also proven effective in the relief of acute migraine pain[2]
- Onset of pain relief within 15 minutes[1,2]

STADOL® NS™
(butorphanol tartrate) Nasal Spray

Acute Pain Relief, Delivered in Minutes

*Across all clinical trials, including STADOL® Injectable and STADOL NS.[3] Patients should not perform potentially hazardous tasks (eg, driving, operating machinery). Alcohol should not be consumed while using STADOL NS.

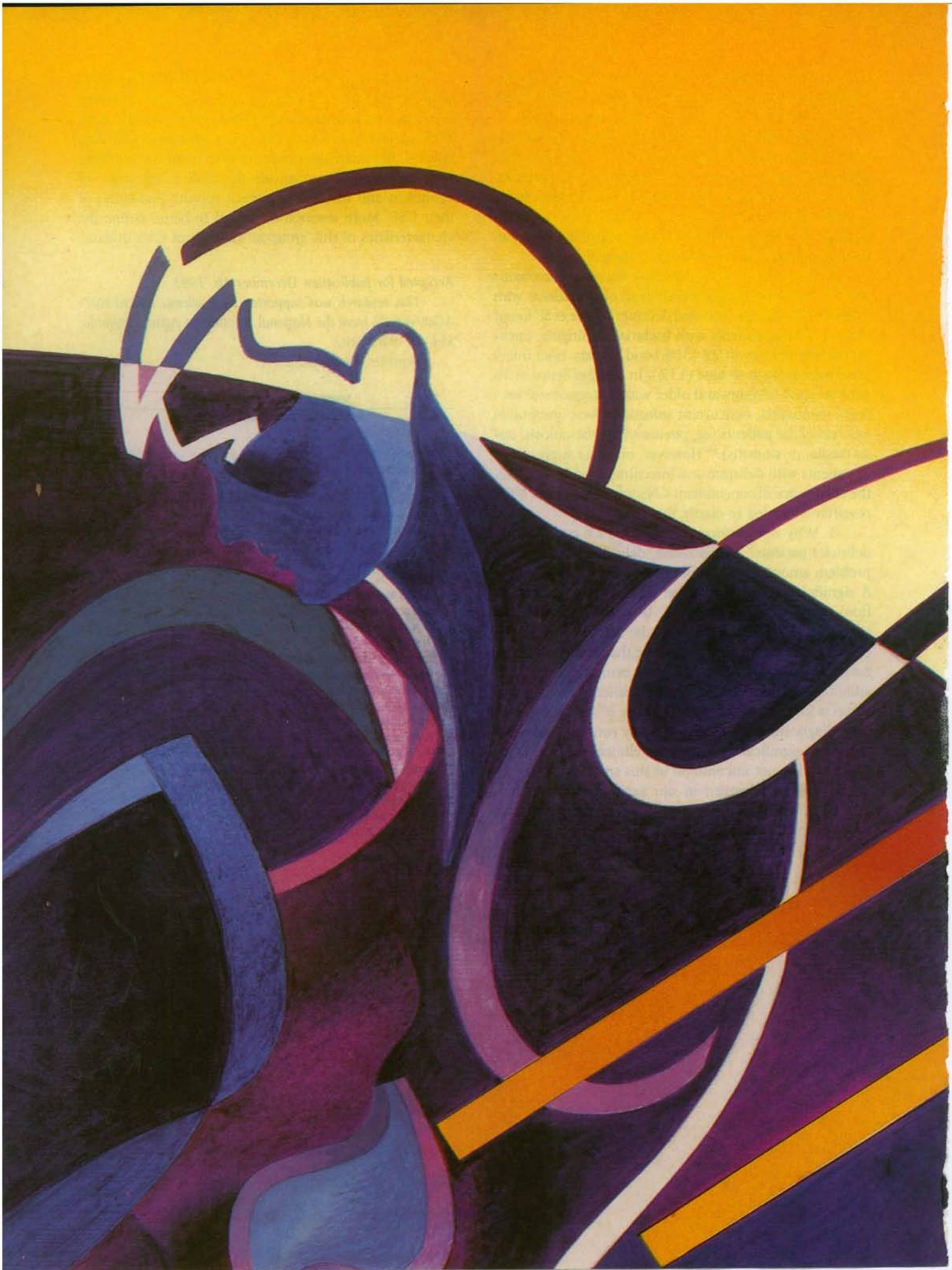
C-K62-6-92

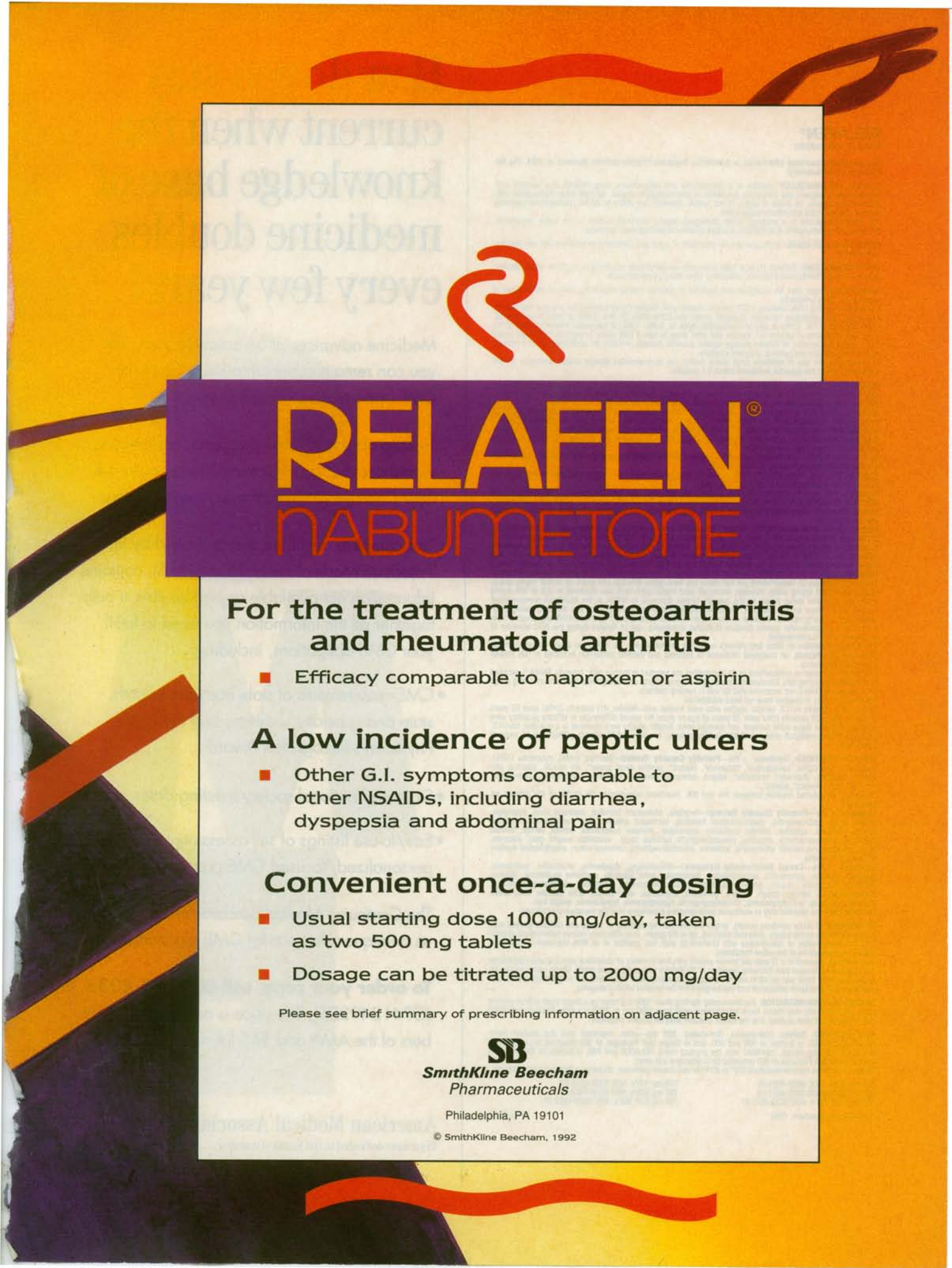
1. Schwesinger WH, Reynolds JC, Harshaw DH, Frakes LA. Transnasal butorphanol and intramuscular meperidine in the treatment of postoperative pain. *Advances in Therapy.* 1992;9:123-129.

2. Diamond S, Freitag FG, Diamond ML, Urban G. Transnasal butorphanol in the treatment of migraine headache pain. *Headache Quarterly.* 1992;3:160-167.

3. STADOL® NS™ package insert.

Please see brief summary of prescribing information on following page.




RELAFEN®
NABUMETONE
For the treatment of osteoarthritis and rheumatoid arthritis
Efficacy comparable to naproxen or aspirin
A low incidence of peptic ulcers
Other G.I. symptoms comparable to other NSAIDs, including diarrhea, dyspepsia and abdominal pain
Convenient once-a-day dosing
Usual starting dose 1000 mg/day, taken as two 500 mg tablets
Dosage can be titrated up to 2000 mg/day
Please see brief summary of prescribing information on adjacent page.
SB
SmithKline Beecham
Pharmaceuticals
Philadelphia, PA 19101
© SmithKline Beecham, 1992

RELAFEN®
brand of nabumetone

See complete prescribing information in SmithKline Beecham Pharmaceuticals literature or *PDR*. The following is a brief summary.

CLINICAL PHARMACOLOGY: *Relafen* is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic and antipyretic properties in pharmacologic studies. As with other nonsteroidal anti-inflammatory agents, its mode of action is not known. However, the ability to inhibit prostaglandin synthesis may be involved in the anti-inflammatory effect.
The parent compound is a prodrug, which undergoes hepatic biotransformation to the active component, 6-methoxy-2-naphthylacetic acid (6MNA), a potent inhibitor of prostaglandin synthesis.

INDICATIONS AND USAGE: Acute and chronic treatment of signs and symptoms of osteoarthritis and rheumatoid arthritis.

CONTRAINDICATIONS: Patients (1) who have previously exhibited hypersensitivity to it; (2) in whom *Relafen*, aspirin or other NSAIDs induce asthma, urticaria or other allergic-type reactions.

WARNINGS: Remain alert for ulceration and bleeding in patients treated chronically, even in the absence of previous G.I. tract symptoms.
In controlled clinical trials involving 1,677 patients treated with *Relafen* (1,140 followed for one year and 927 for two years), the cumulative incidence of peptic ulcers was 0.3% (95% CI; 0%, 0.6%) at three to six months, 0.5% (95% CI; 0.1%, 0.9%) at one year and 0.8% (95% CI; 0.3%, 1.3%) at two years. Inform patients of the signs and symptoms of serious G.I. toxicity and what steps to take if they occur. In patients with active peptic ulcer, weigh the benefits of *Relafen* therapy against possible hazards, institute an appropriate ulcer treatment regimen and monitor the patients' progress carefully.
In considering the use of relatively large doses (within the recommended dosage range), anticipate benefit sufficient to offset the potential increased risk of G.I. toxicity.

PRECAUTIONS: Because nabumetone undergoes extensive hepatic metabolism, no adjustment of *Relafen* dosage is generally necessary in patients with renal insufficiency. However, as with all NSAIDs, monitor patients with impaired renal function more closely than patients with normal renal function.
Evaluate patients with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, for evidence of the development of a more severe hepatic reaction while on *Relafen* therapy. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue *Relafen*. Use *Relafen* cautiously in patients with severe hepatic impairment.
As with other NSAIDs, use *Relafen* cautiously in patients with a history of congestive heart failure, hypertension or other conditions predisposing to fluid retention.
Based on U.V. light photosensitivity testing, *Relafen* may be associated with more reactions to sun exposure than might be expected based on skin tanning types.
Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS and ADVERSE REACTIONS) and likely benefits of NSAID treatment, particularly when the drugs are used for less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both the patient and the physician.
Exercise caution when administering *Relafen* with warfarin since interactions have been seen with other NSAIDs.
In two-year studies conducted in mice and rats, nabumetone had no statistically significant tumorigenic effect. Nabumetone did not show mutagenic potential in the Ames test and mouse micronucleus test *in vivo*. However, nabumetone- and 6MNA-treated lymphocytes in culture showed chromosomal aberrations at 80mcg/mL and higher concentrations (equal to the average human exposure to *Relafen* at the maximum recommended dose). Nabumetone did not impair fertility of male or female rats treated orally at doses of 320 mg/kg/day before mating.
Pregnancy Category C: Nabumetone did not cause any teratogenic effect in rats given up to 400 mg/kg and in rabbits up to 300 mg/kg orally. However, increased post-implantation loss was observed in rats at 100 mg/kg orally and at higher doses (equal to the average human exposure to 6MNA at the maximum recommended human dose). There are no adequate, well-controlled studies in pregnant women. Use the drug during pregnancy only if clearly needed. Because of the known effect of prostaglandin-synthesis-inhibiting drugs on the human fetal cardiovascular system (closure of ductus arteriosus), use of *Relafen* during the third trimester of pregnancy is not recommended.
The effects of *Relafen* on labor and delivery in women are not known. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats treated throughout pregnancy.
It is not known whether nabumetone or its metabolites are excreted in human milk; however, 6MNA is excreted in the milk of lactating rats. Because of the possible adverse effects of prostaglandin-synthesis-inhibiting drugs on neonates, *Relafen* is not recommended for use in nursing mothers.
Safety and efficacy in children have not been established.
Of the 1,677 patients in U.S. clinical studies who were treated with *Relafen*, 411 patients (24%) were 65 years of age or older; 22 patients (1%) were 75 years of age or older. No overall differences in efficacy or safety were observed between these older patients and younger ones. Similar results were observed in a one-year, non-U.S. postmarketing surveillance study of 10,800 *Relafen* patients, of whom 4,577 patients (42%) were 65 years of age or older.

ADVERSE REACTIONS: Incidence ≥1%—Probably Causally Related—Diarrhea (14%), dyspepsia (13%), abdominal pain (12%), constipation*, flatulence*, nausea*, positive stool guaiac*, dry mouth, gastritis, stomatitis, vomiting, dizziness*, headache*, fatigue, increased sweating, insomnia, nervousness, somnolence, pruritus*, rash*, tinnitus*, edema*.
*Incidence of reported reaction between 3% and 9%. Reactions occurring in 1% to 3% of the patients are unmarked.
Incidence <1%—Probably Causally Related†—Anorexia, cholestatic jaundice, duodenal ulcer, dysphagia, gastric ulcer, gastroenteritis, gastrointestinal bleeding, increased appetite, liver function abnormalities, melena, asthenia, agitation, anxiety, confusion, depression, malaise, paresthesia, tremor, vertigo, bullous eruptions, photosensitivity, urticaria, pseudoporphyria cutanea tarda, vasculitis, weight gain, dyspnea, *hypersensitivity pneumonitis*, albuminuria, azotemia, *interstitial nephritis*, abnormal vision, *anaphylactoid reaction*, angioneurotic edema.
Incidence <1%—Causal Relationship Unknown†—Bilirubinuria, duodenitis, eructation, gallstones, gingivitis, glossitis, pancreatitis, rectal bleeding, nightmares, acne, alopecia, *erythema multiforme, Stevens-Johnson Syndrome*, angina, arrhythmia, hypertension, myocardial infarction, palpitations, syncope, thrombophlebitis, asthma, cough, dysuria, hematuria, impotence, renal stones, taste disorder, fever, chills, anemia, leukopenia, granulocytopenia, thrombocytopenia, hyperglycemia, hypokalemia, weight loss.
†Adverse reactions reported only in worldwide postmarketing experience or in the literature are italicized.

OVERDOSAGE: If acute overdose occurs, empty the stomach by vomiting or lavage and institute general supportive measures as necessary. Activated charcoal, up to 60 grams, may effectively reduce nabumetone absorption. Coadministration of nabumetone with charcoal to man has resulted in an 80% decrease in maximum plasma concentrations of the active metabolite.
One overdose occurred in a 17-year-old female patient who had a history of abdominal pain and was hospitalized for increased abdominal pain following ingestion of 30 *Relafen* tablets (15 grams total). Stools were negative for occult blood and there was no fall in serum hemoglobin concentration. The patient had no other symptoms. She was given an H_2-receptor antagonist and discharged from the hospital without sequelae.

DOSAGE AND ADMINISTRATION: Recommended starting dose: 1000 mg taken as a single dose with or without food. Some patients may obtain more symptomatic relief from 1500 mg to 2000 mg daily. Dosages over 2000 mg daily have not been studied. Use the lowest effective dose for chronic treatment.

HOW SUPPLIED: Tablets: Oval-shaped, film-coated: 500 mg—white, imprinted with the product name RELAFEN and 500, in bottles of 100 and 500, and in Single Unit Packages of 100 (intended for institutional use only); 750 mg—beige, imprinted with the product name RELAFEN and 750, in bottles of 100 and 500, and in Single Unit Packages of 100 (intended for institutional use only).
Store at controlled room temperature (59° to 86°F) in well-closed container; dispense in light-resistant container.

500 mg 100's: NDC 0029-4851-20
500 mg 500's: NDC 0029-4851-25
500 mg SUP 100's: NDC 0029-4851-21
750 mg 100's: NDC 0029-4852-20
750 mg 500's: NDC 0029-4852-25
750 mg SUP 100's: NDC 0029-4852-21

BRS-RL:L3

FREEDOM FROM PAIN!

Extra strength pain relief free of extra prescribing restrictions.

- Telephone prescribing in most states
- Up to five refills in 6 months
- No triplicate Rx required

15 years of proven clinical experience

- Effective central and peripheral pain relief.
- Excellent patient acceptance—nausea, sedation and constipation have rarely been reported.[1]
- Four to six hours of extra strength pain relief from a single dose.
- The heritage of VICODIN®* — over one billion doses prescribed.[2]
- The 8th most frequently prescribed medication in America.[2]

vicodin ES® (III)

(hydrocodone bitartrate 7.5mg [Warning: May be habit forming] and acetaminophen 750mg)

Extra strength pain relief you can phone in.

[1] Data on file, Knoll Pharmaceutical Company
[2] Standard industry new prescription audit.
*(hydrocodone bitartrate 5mg [Warning: May be habit forming] and acetaminophen 500 mg)

V3087/10-92

Printed in U.S.A.

Maintain control of your patient's pain therapy.

vicodin ES®

(hydrocodone bitartrate 7.5mg (Warning: May be habit forming) and acetaminophen 750mg)

It's your prescription— not a suggestion.

INDICATIONS AND USAGE: For the relief of moderate to moderately severe pain. **CONTRAINDICATIONS:** Hypersensitivity to acetaminophen or hydrocodone. **WARNINGS: Respiratory Depression:** At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression. **Head Injury and Increased Intracranial Pressure:** The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries. **Acute Abdominal Conditions:** The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions. **PRECAUTIONS: Special Risk Patients:** VICODIN/VICODIN ES Tablets should be used with caution in elderly or debilitated patients and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. **Cough Reflex:** Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when VICODIN/VICODIN ES Tablets are used postoperatively and in patients with pulmonary disease. **Drug Interactions:** Patients receiving other narcotic analgesics, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with VICODIN/VICODIN ES Tablets may exhibit an additive CNS depression. The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone. The concurrent use of anticholinergics with hydrocodone may produce paralytic ileus. **Usage in Pregnancy: Teratogenic Effects:** Pregnancy Category C. Hydrocodone has been shown to be teratogenic in hamsters when given in doses 700 times the human dose. There are no adequate and well-controlled studies in pregnant women. VICODIN/VICODIN ES Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nonteratogenic effects:** Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. **Labor and Delivery:** Administration of VICODIN/VICODIN ES Tablets to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from VICODIN/VICODIN ES Tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** Safety and effectiveness in children have not been established. **ADVERSE REACTIONS:** The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients and some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include: **Central Nervous System:** Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence and mood changes. **Gastrointestinal System:** The antiemetic phenothiazines are useful in suppressing the nausea and vomiting which may occur (see above); however, some phenothiazine derivatives seem to be antianalgesic and to increase the amount of narcotic required to produce pain relief, while other phenothiazines reduce the amount of narcotic required to produce a given level of analgesia. Prolonged administration of VICODIN/VICODIN ES Tablets may produce constipation. **Genitourinary System:** Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported. **Respiratory Depression:** Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing. If significant respiratory depression occurs, it may be antagonized by the use of naloxone hydrochloride. Apply other supportive measures when indicated. **DRUG ABUSE AND DEPENDENCE:** VICODIN/VICODIN ES Tablets are subject to the Federal Controlled Substance Act (Schedule III). Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, VICODIN/VICODIN ES Tablets should be prescribed and administered with caution. **OVERDOSAGE: Acetaminophen Signs and Symptoms:** In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion. **Hydrocodone Signs and Symptoms:** Serious overdose with hydrocodone 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, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

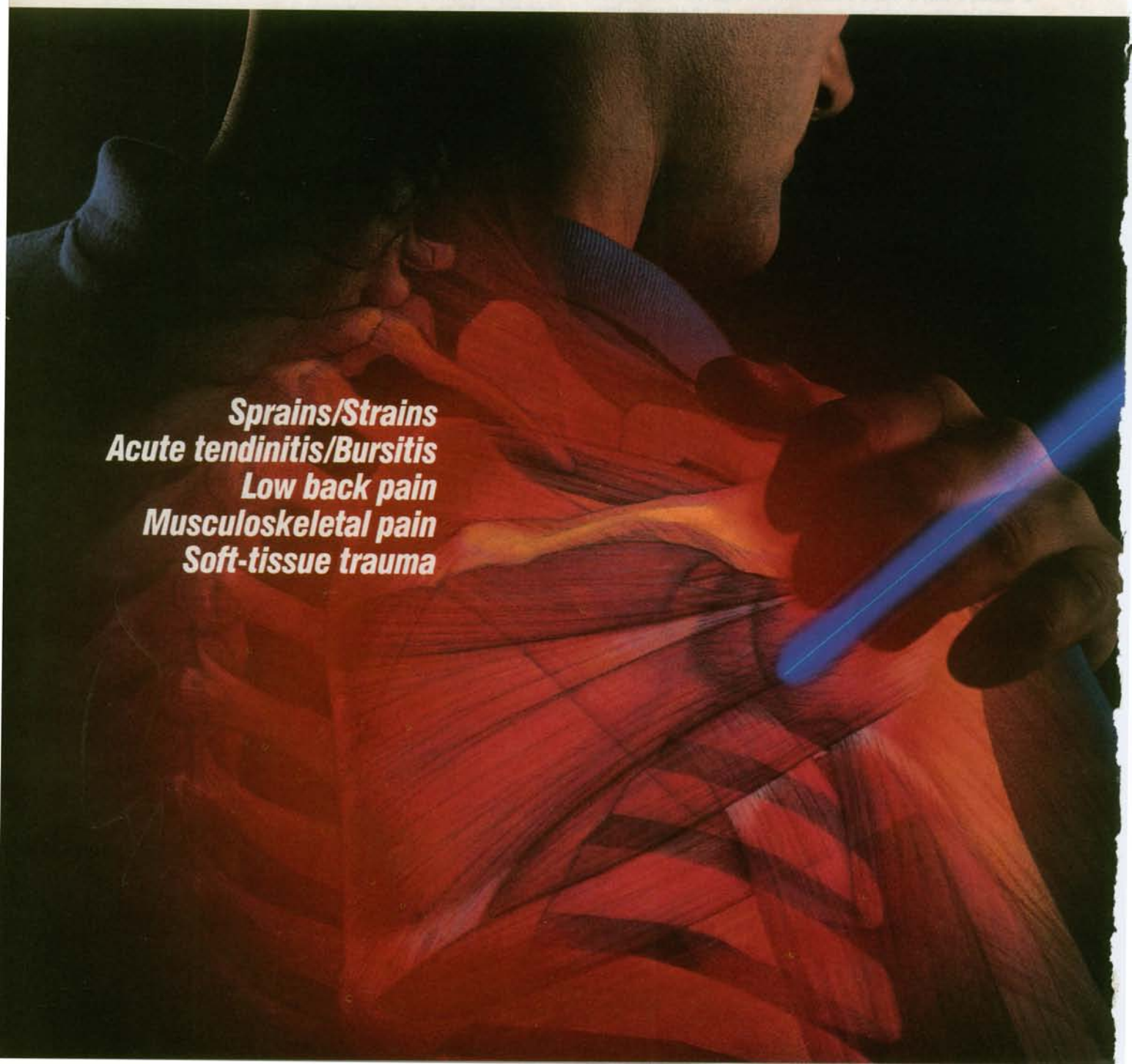
Revised March 1992 5890

Knoll Pharmaceutical Company
30 North Jefferson Road
Whippany, New Jersey 07981

BASF Group

knoll

Fast, effective relief for pain/inflammation.



Fast–pain relief may occur as fast as 20 minutes.

Effective–works at the pain site to provide relief for mild to moderate pain/inflammation.

Anti-inflammatory–nonsteroidal anti-inflammatory action helps patients return to normal activity.

Well tolerated–no narcotic-related side effects; no addiction potential.

As with other NSAIDs, the most frequent complaints are gastrointestinal. See Warnings, Precautions, and Adverse Reactions sections of prescribing information.

Convenient dosing–recommended starting dose is 550 mg, followed by 275 mg every 6 to 8 hours, as required. Total daily dose should not exceed 1375 mg.

Fast Relief. Fast Recovery.

550 MG TABLETS **Anaprox®DS** 275 MG TABLETS **Anaprox®**

(NAPROXEN SODIUM)

SYNTEX

SYNTEX PUERTO RICO, INC.
HUMACAO, PR. 00661

For brief summary of prescribing information, please see next page.

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.

165 Cadman Plaza East, Brooklyn, New York 11201
(718) 596-1043 • Fax (718) 802-1039

HELP PREVENT HEART ATTACK WITH A STROKE.

The back stroke. The crawl. The butterfly. It doesn't matter which you choose, as long as you do it up to 40 minutes, 3 to 4 times a week. Or try cycling or jogging. Any type of aerobic exercise program can help reduce your risk of heart attack and stroke. The only hard part is diving in. To learn more, contact the American Heart Association, 7272 Greenville Avenue, Box 47, Dallas, TX 75231-4596.

You can help prevent heart disease and stroke.
We can tell you how.

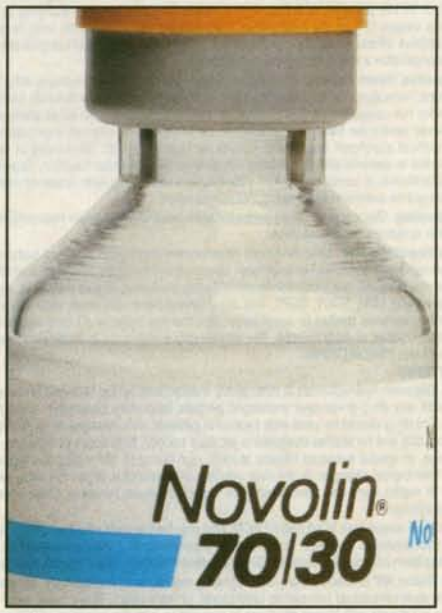
American Heart Association

Novo Nordisk

NOVOLIN® 70/30

70% NPH, Human Insulin Isophane Suspension and
30% Regular, Human Insulin Injection (recombinant DNA origin)

Combining Control and Confidence



CONTROL

- Premixed to provide rapid onset and sustained duration

CONFIDENCE

- Premixed so patients don't have to mix for themselves
- Simple, B.I.D. dosage

WARNING: ANY CHANGE IN INSULIN SHOULD BE MADE CAUTIOUSLY AND ONLY UNDER MEDICAL SUPERVISION.

Now, *for hypertension*
Once-a-day

DILACOR XR®
(diltiazem HCl) EXTENDED RELEASE CAPSULES

120 mg

180 mg

240 mg

24-HOUR DELIVERY FOR 24-HOUR SECURITY

BRIEF SUMMARY

CONTRAINDICATIONS

Diltiazem hydrochloride 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 mmHg systolic); (4) patients who have demonstrated hypersensitivity to the drug; and (5) patients with acute myocardial infarction and pulmonary congestion as documented by X-ray on admission.

WARNINGS

1. Cardiac Conduction. Diltiazem hydrochloride 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 (22 of 10,119 patients, or 0.2%); 41% of these 22 patients were receiving concomitant ß-adrenoceptor antagonists versus 17% of the total group. 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 60 mg dose of diltiazem.

2. 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 of 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of diltiazem hydrochloride in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

3. Hypotension. Decreases in blood pressure associated with diltiazem hydrochloride therapy may occasionally result in symptomatic hypotension.

4. Acute Hepatic Injury. Mild elevations of serum 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 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 6 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to diltiazem is uncertain in some cases, but probable in some others (see PRECAUTIONS).

PRECAUTIONS

General. Diltiazem hydrochloride is extensively metabolized by the liver and is excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters 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 the 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) may be transient and may disappear despite continued use of diltiazem hydrochloride. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Although Dilacor XR® utilizes a slowly disintegrating matrix, caution should still be used in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been no reports of obstructive symptoms in patients with known strictures in association with the ingestion of Dilacor XR®.

Information for Patients. Dilacor XR® capsules should be taken on an empty stomach. Patients should be cautioned that the Dilacor XR® capsules should not be opened, chewed or crushed, and should be swallowed whole.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving diltiazem hydrochloride concomitantly with any 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 diltiazem hydrochloride (see WARNINGS). As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem hydrochloride undergoes biotransformation by cytochrome P-450 mixed function oxidase. Co-administration of diltiazem hydrochloride with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, such as cyclosporin, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered diltiazem hydrochloride to maintain optimum therapeutic blood levels.

Beta-Blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of diltiazem hydrochloride 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 diltiazem hydrochloride concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and the bioavailability of propranolol was increased approximately 50%. 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 1,200 mg per day and diltiazem 60 mg per day. 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 diltiazem hydrochloride 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 diltiazem hydrochloride 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 channel blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and an 18-month study in mice 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 male or female rats at oral doses 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 4 to 6 times (depending on species) the upper limit of the optimum dosage range in clinical trials (480 mg q.d. or 8 mg/kg q.d. for a 60 kg patient) has resulted in embryo and fetal lethality. These studies have revealed, in one species or another, a propensity to cause abnormalities of the skeleton, heart, retina, and tongue. Also observed were reductions in early individual pup weights and pup survival, prolonged delivery and increased incidence of stillbirths.

There are no well-controlled studies in pregnant women; therefore, use diltiazem hydrochloride 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 diltiazem hydrochloride 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 to diltiazem hydrochloride have been rare in studies with other formulations, as well as with Dilacor XR®. It should be recognized, however, that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The most common adverse events (frequency ≥1%) in placebo-controlled, clinical hypertension studies with Dilacor XR® using daily doses up to 540 mg are listed in the table below with placebo-treated patients included for comparison.

MOST COMMON ADVERSE EVENTS
IN DOUBLE-BLIND, PLACEBO-CONTROLLED HYPERTENSION TRIALS*

Adverse Events (COSTART Term)	Dilacor XR® n=303 # pts (%)	Placebo n=87 # pts (%)
rhinitis	29 (9.6)	7 (8.0)
headache	27 (8.9)	12 (13.8)
pharyngitis	17 (5.6)	4 (4.6)
constipation	11 (3.6)	2 (2.3)
cough increase	9 (3.0)	2 (2.3)
flu syndrome	7 (2.3)	1 (1.1)
edema, peripheral	7 (2.3)	0 (0.0)
myalgia	7 (2.3)	0 (0.0)
diarrhea	6 (2.0)	0 (0.0)
vomiting	6 (2.0)	0 (0.0)
sinusitis	6 (2.0)	1 (1.1)
asthenia	5 (1.7)	0 (0.0)
pain, back	5 (1.7)	2 (2.3)
nausea	5 (1.7)	1 (1.1)
dyspepsia	4 (1.3)	0 (0.0)
vasodilatation	4 (1.3)	0 (0.0)
injury, accident	4 (1.3)	0 (0.0)
pain, abdominal	3 (1.0)	0 (0.0)
arthrosis	3 (1.0)	0 (0.0)
insomnia	3 (1.0)	0 (0.0)
dyspnea	3 (1.0)	0 (0.0)
rash	3 (1.0)	1 (1.1)
tinnitus	3 (1.0)	0 (0.0)

*Adverse events occurring in 1% or more of patients receiving Dilacor XR®.

The following additional events (COSTART Terms), listed by body system, were reported infrequently in all subjects and hypertensive patients who received Dilacor XR® (n=425): Cardiovascular: First-degree AV block, arrhythmia, postural hypotension, tachycardia, pallor, palpitations, phlebitis, ECG abnormality, ST elevation; Nervous System: Vertigo, hypertonia, paresthesia, dizziness, somnolence; Digestive System: Dry mouth, anorexia, tooth disorder, eructation; Skin and Appendages: Sweating, urticaria, skin hypertrophy (nevus); Respiratory System: Epistaxis, bronchitis, respiratory disorder; Urogenital System: Cystitis, kidney calculus, impotence, dysmenorrhea, vaginitis, prostate disease; Metabolic and Nutritional Disorders: Gout, edema; Musculoskeletal System: Arthralgia, bursitis, bone pain; Hemic and Lymphatic Systems: Lymphadenopathy; Body as a Whole: Pain, unevaluable reaction, neck pain, neck rigidity, fever, chest pain, malaise; Special Senses: Amblyopia (blurred vision), ear pain.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem hydrochloride has been limited. The administration of ipecac to induce vomiting and activated charcoal to reduce drug absorption have been advocated as initial means of intervention. In addition to gastric lavage, the following measures should also be considered:

Bradycardia: Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

High-Degree AV Block: Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.

Cardiac Failure: Administer inotropic agents (dopamine or dobutamine) and diuretics.

Hypotension: Vasopressors (*e.g.* dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation as well as the judgment and experience of the treating physician.

Due to extensive metabolism, plasma concentrations after a standard dose of diltiazem can vary over tenfold, which significantly limits their value in evaluating cases of overdosage.

Charcoal hemoperfusion has been used successfully as an adjunct therapy to hasten drug elimination. Overdoses with as much as 10.8 gm of oral diltiazem have been successfully treated using appropriate supportive care.

CAUTION: FEDERAL (U.S.A.) LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

Please see product circular for full prescribing information.

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eference: 1. Graney WF: Clinical experience with a once-daily, extended-release formulation of diltiazem in the treatment of hypertension. *Am J Med* 1992;93 (Suppl 2A): 56S-64S.

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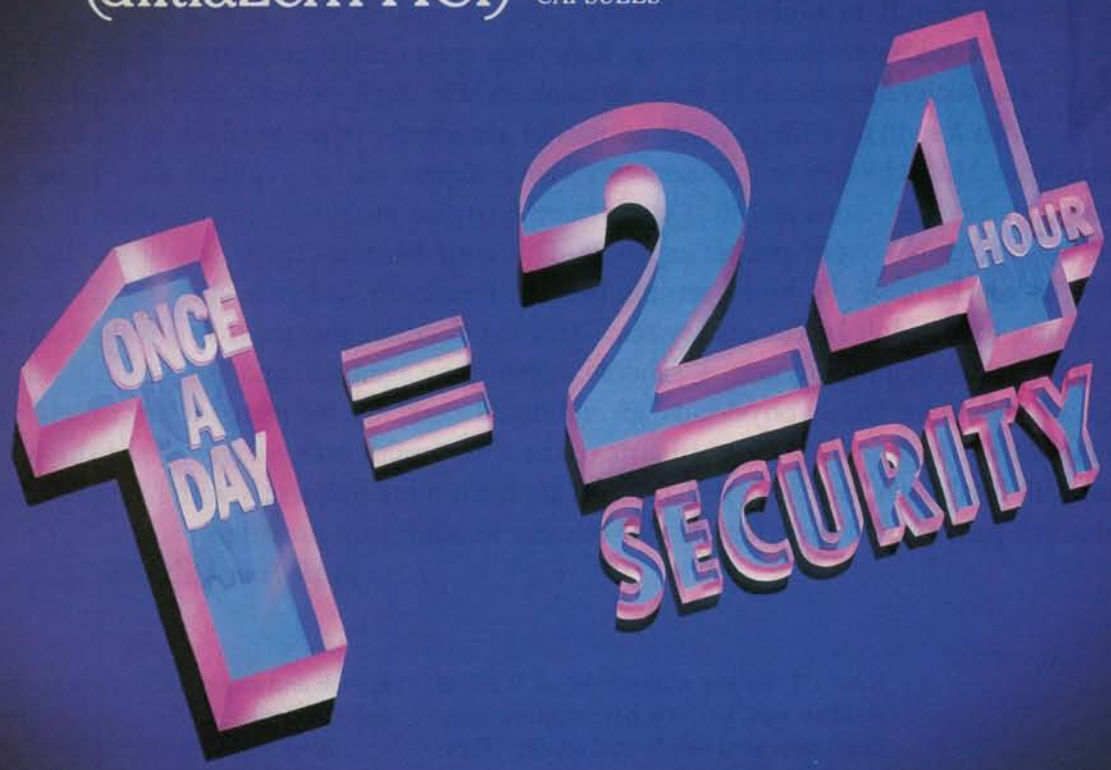

DILACOR XR effectively lowers blood pressure for 24 hours in the majority of patients[1]

DILACOR XR offers the classic diltiazem safety profile across the entire dosing range[1]

DILACOR XR now makes diltiazem a more affordable option for hypertension*

Please see adjacent page for brief summary of prescribing information.

*Based on average wholesale price (approximate cost to the pharmacist) as listed in *1992 Drug Topics® Red Book® Update.* Montvale, NJ, Medical Economics Co. Inc.; December 1992.

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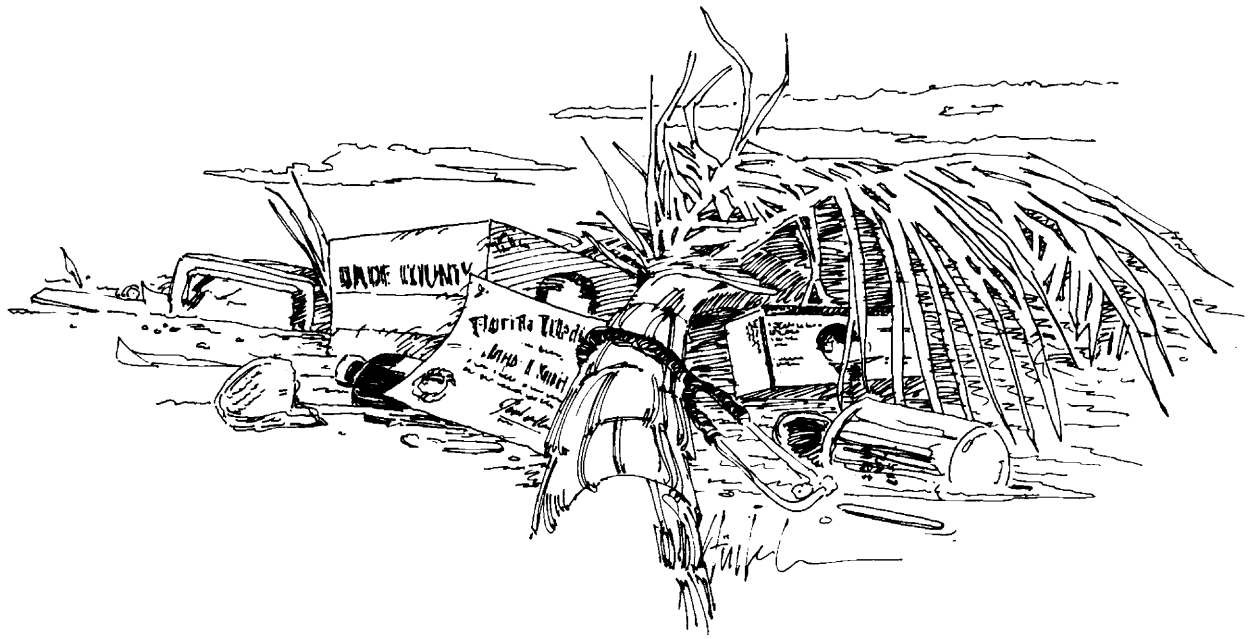

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Send contributions payable to: *Florida Medical Foundation, Hurricane Relief Fund, PO Box 2411, Jacksonville, FL 32203.* Or contact the Florida Medical Association, 904 356-1571.

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