Today's hypertensives with new concerns...

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.[1-3]

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. 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. **2.** 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. **3.** 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

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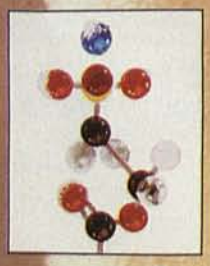
A method no soap can claim

Dove® is special. It has a unique, non-soap surfactant that replaces soap's alkaline end group with a milder isethionyl radical. This results in a non-soap, pH-neutral formulation that also contains 1/4 moisturizing cream.



A mildness no soap can touch

Dove Bar's unique, non-soap formula is milder to skin than *any* soap. Clinical trials prove it. Dove Bar causes significantly less irritation and dryness—and it helps the skin retain needed moisture, too. The result: Dove leaves skin softer and smoother than skin washed with soap. So recommend Dove—for mildness no soap can touch.

Beauty Bar and Beauty Wash
Available in original and Unscented

MILDER TO SKIN THAN SOAP

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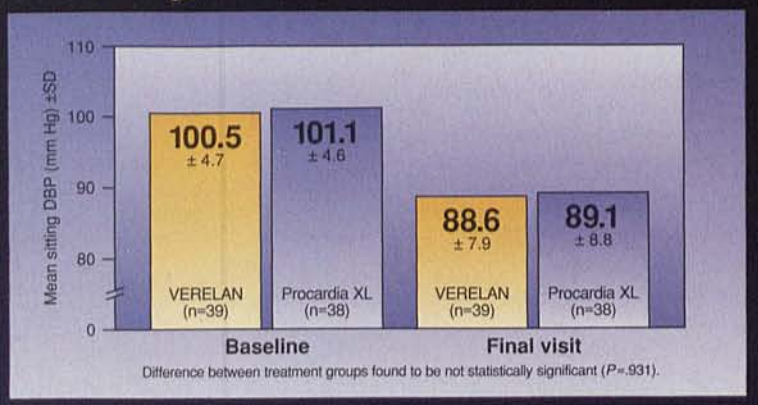
AMP

References: 1. Levy B, Rosenberg LN, Colasante DA. A comparison of VERELAN® and Procardia® XL in the treatment of patients with mild to moderate hypertension. American College of Clinical Pharmacology. 21st Annual Meeting, 1992. Abstract. 2. Further analysis of Levy B, et al. (See reference 1.) Data on file. Lederle Laboratories, Pearl River, NY.

VERELAN

AS EFFECTIVE AS PROCARDIA XL®* IN REDUCING BP AT THE 24TH HOUR[1,2]

Reduction in mean DBP measured 24±2 hours after dosing



Results of a 12-week, randomized, double-blind, parallel, comparative study of patients with mild-to-moderate hypertension in 10 study sites nationwide. Patients not controlled on VERELAN 240 mg/day were titrated to 360 mg/day and, if needed, 480 mg/day; patients not controlled on Procardia XL 30 mg/day were titrated to 60 mg/day and, if needed, 90 mg/day. There was no significant difference between groups in the number of titrations to goal DBP (<90 mm Hg).

**Procardia XL is a registered trademark of Pfizer Inc.*

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 on adjacent page.

ONCE-A-DAY

VERELAN®

Verapamil HCl 120 mg 180 mg 240 mg

PELLET-FILLED CAPSULES

TAGAMET® (brand of cimetidine)

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

Indications and Usage: *1) Short-term treatment of active duodenal ulcer; (2) maintenance therapy for duodenal ulcer patients at reduced dosage after healing of active ulcer; (3) short-term treatment of active benign gastric ulcer; (4) erosive gastroesophageal reflux disease; (5) prevention of upper gastrointestinal bleeding in critically ill patients; (6) treatment of pathological hypersecretory conditions.*

Contraindications: *Tagamet is contraindicated for patients known to have hypersensitivity to the product.*

Precautions: *Rare instances of cardiac arrhythmias and hypotension have been reported following the rapid administration of Tagamet (cimetidine hydrochloride) injection by intravenous bolus.*

Symptomatic response to Tagamet therapy does not preclude the presence of a gastric malignancy. There have been rare reports of transient healing of gastric ulcers despite subsequently documented malignancy.

Reversible confusional states have been observed on occasion, predominantly in severely ill patients.

Tagamet has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, nifedipine, chlordiazepoxide, diazepam, certain tricyclic antidepressants, lidocaine, theophylline and metronidazole. Clinically significant effects have been reported with the warfarin anticoagulants; therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when Tagamet is administered concomitantly. Interaction with phenytoin, lidocaine and theophylline has also been reported to produce adverse clinical effects.

However, a crossover study in healthy subjects receiving either Tagamet 300 mg q.i.d. or 800 mg h.s. concomitantly with a 300 mg b.i.d. dosage of theophylline (Theo-Dur®, Key Pharmaceuticals, Inc.) demonstrated less alteration in steady-state theophylline peak serum levels with the 800 mg h.s. regimen, particularly in subjects aged 54 years and older. Data beyond ten days are not available. (Note: All patients receiving theophylline should be monitored appropriately, regardless of concomitant drug therapy.)

In a 24-month toxicity study in rats, at dose levels approximately 8 to 48 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving Tagamet.

A weak antiandrogenic effect has been demonstrated in animals. In human studies, Tagamet has been shown to have no effect on spermatogenesis, sperm count, motility, morphology or in vitro fertilizing capacity.

Pregnancy Category B: Reproduction studies have been performed in rats, rabbits and mice at doses up to 40 times the normal human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Tagamet. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Lack of experience to date precludes recommending Tagamet for use in children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should not be undertaken by patients taking the drug since cimetidine is secreted in human milk.

Adverse Reactions: *Diarrhea, dizziness, somnolence, headache. Reversible confusional states (e.g., mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation), predominantly in severely ill patients, have been reported. Reversible impotence in patients with pathological hypersecretory disorders receiving Tagamet, particularly in high doses for at least 12 months, has been reported. The incidence of impotence in large-scale surveillance studies at regular doses has not exceeded that commonly reported in the general population. Gynecomastia has been reported in patients treated for one month or longer. Decreased white blood cell counts in Tagamet-treated patients (approximately 1 per 100,000 patients), including agranulocytosis (approximately 3 per million patients), have been reported, including a few reports of recurrence on rechallenge. Most of these reports were in patients who had serious concomitant illnesses and received drugs and/or treatment known to produce neutropenia. Thrombocytopenia (approximately 3 per million patients) and, very rarely, cases of pancytopenia or aplastic anemia have also been reported. As with some other H_2-receptor antagonists, there have been extremely rare reports of immune hemolytic anemia. Dose-related increases in serum transaminase have been reported. Reversible adverse hepatic effects, cholestatic or mixed cholestatic-hepatocellular in nature, have been reported rarely. Because of the predominance of cholestatic features, severe parenchymal injury is considered highly unlikely. A single case of biopsy-proven periportal hepatic fibrosis in a patient receiving Tagamet has been reported. Small, possibly dose-related increases in plasma creatinine have been reported. Rare cases of fever, interstitial nephritis, urinary retention, pancreatitis and allergic reactions, including anaphylaxis and hypersensitivity vasculitis, have been reported. Rare cases of bradycardia, tachycardia and A-V heart block have been reported with H_2-receptor antagonists. Reversible arthralgia, myalgia and exacerbation of joint symptoms in patients with preexisting arthritis have been reported rarely. Rare cases of polymyositis have been reported, but no causal relationship has been established. Mild rash and, very rarely, cases of severe generalized skin reactions (e.g., Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis and generalized exfoliative erythroderma) have been reported with H_2-receptor antagonists. Reversible alopecia has been reported very rarely.*

How Supplied: Tablets: *200 mg tablets in bottles of 100; 300 mg tablets in bottles of 100 and Single Unit Packages of 100 (intended for institutional use only); 400 mg tablets in bottles of 60 and Single Unit Packages of 100 (intended for institutional use only), and 800 mg Tiltab® tablets in bottles of 30 and Single Unit Packages of 100 (intended for institutional use only).*

Liquid: *300 mg/5 mL, in 8 fl oz (237 mL) amber glass bottles and in single-dose units (300 mg/5 mL), in packages of 10 (intended for institutional use only).*

Injection:
Vials: *300 mg/2 mL in single-dose vials, in packages of 25, and in 8 mL multi-dose vials, in packages of 10 and 25.*

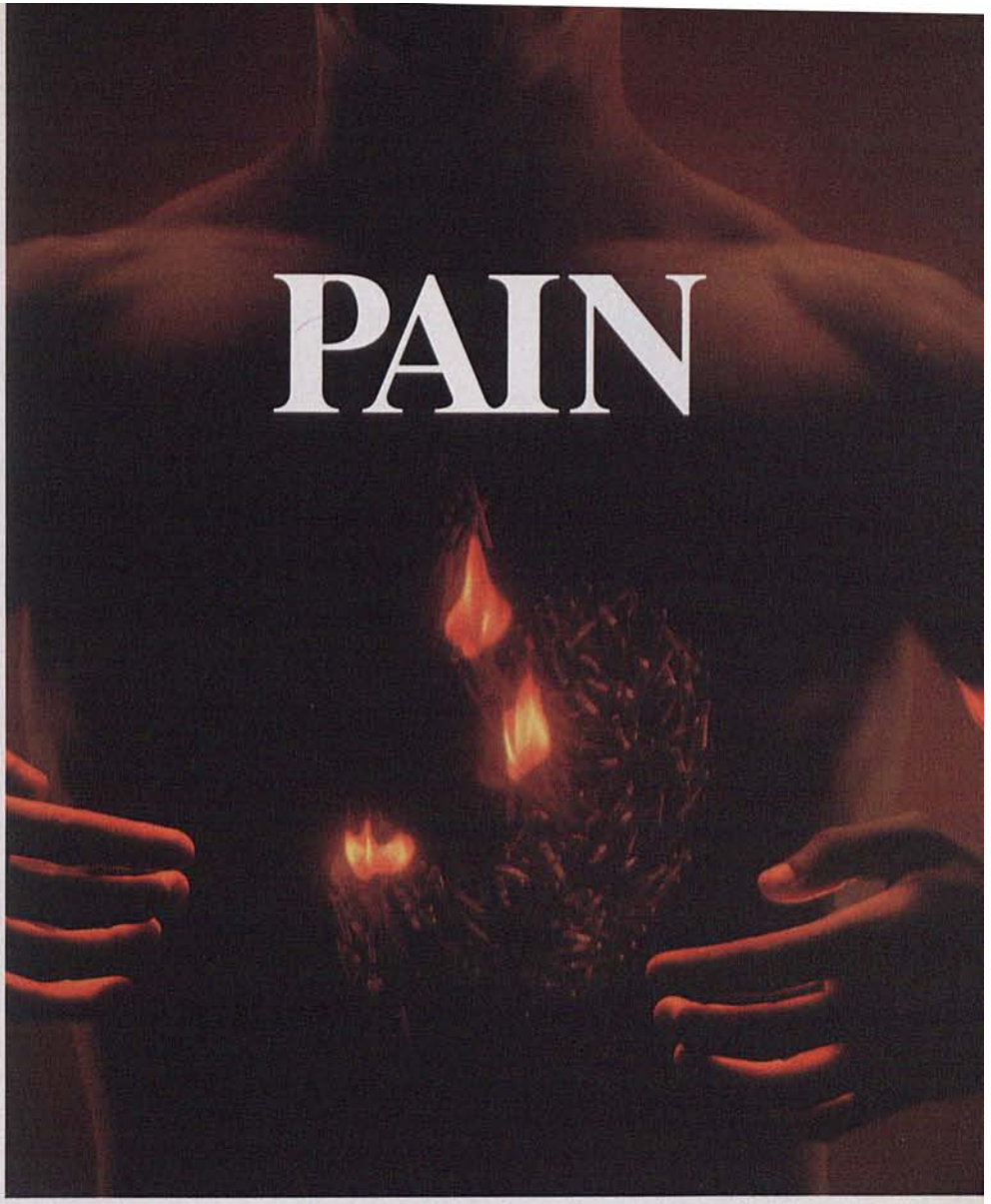
Single-Dose Premixed Plastic Containers: *300 mg in 50 mL of 0.9% Sodium Chloride in single-dose plastic containers, in packages of 4 units. No preservative has been added.*

Exposure of the premixed product to excessive heat should be avoided. It is recommended the product be stored at controlled room temperature. Brief exposure up to 40°C does not adversely affect the premixed product.

ADD-Vantage® Vials: *300 mg/2 mL in single-dose ADD-Vantage® Vials, in packages of 25.*

Tagamet (cimetidine hydrochloride) Injection premixed in single-dose plastic containers is manufactured for SmithKline Beecham Pharmaceuticals by Baxter Healthcare Corporation, Deerfield, IL 60015.

BRS-TG:LB7



RELIEF

Put out the fire *fast* with Tagamet®

In acute duodenal ulcer:
400 mg b.i.d./800 mg Tiltab® Tablets h.s.

In erosive esophagitis: 800 mg b.i.d.

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ONCE DAILY
Nasacort® Nasal Inhaler
(triamcinolone acetonide)

[na ' za-cort]
Triamcinolone Acetonide Nasal Inhaler
For Intranasal Use Only
Shake Well Before Using

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.

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 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/m²/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/m²/day). However, a few female rats which received maternally toxic doses of 8 or 15 mcg/kg/day (60 mcg/m²/day or 110 mcg/m²/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/m²/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/m²/day and 7.0 mcg/m²/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/m²/day in the rat and 320, 640 and 1280 mcg/m²/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/m²/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.

1. 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. Accepted for publication. 2. Data on file, Rhône-Poulenc Rorer Pharmaceuticals Inc.*

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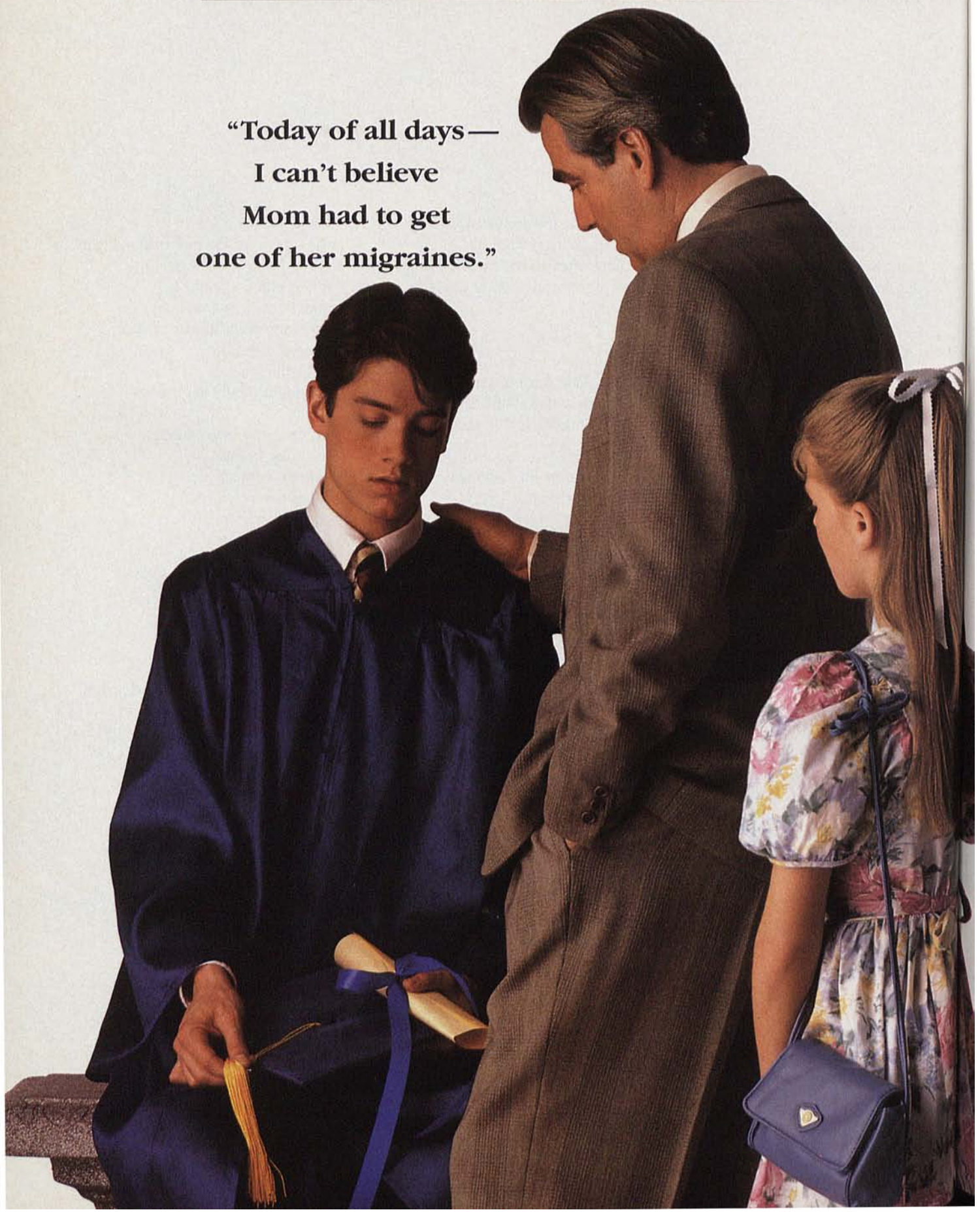
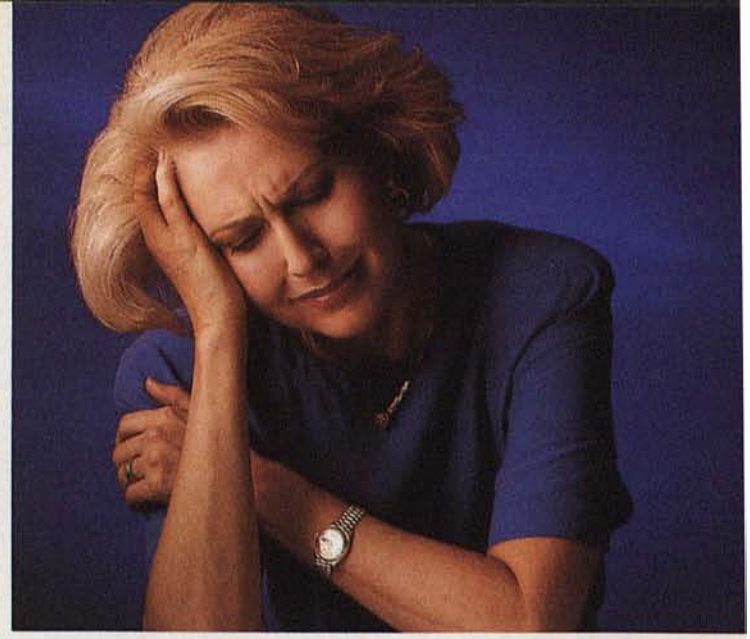
A MIGRAINE DILEMMA



"I'd give anything to be with Scott today, but what could I do? Between the pain and the nausea, I can barely move."



Migraine is more than a headache.
Recent research has revealed that migraine is a complex, multisymptom disorder of neurobiological origin.[1,2] Although various theories have been proposed regarding the exact physiological mechanism of migraine, the practical patient presentation has become increasingly clear: headache is only one aspect of the total migraine symptom complex. Nausea, vomiting, and light and sound sensitivity also contribute to the disabling nature of migraine. And that disability means people in the migraine patient's world suffer too—family, friends, coworkers.

Current estimates indicate that over 11 million Americans suffer from migraine with moderate to severe disability[3]... and the prevalence of migraine is on the rise.[4] Yet, the sad fact is only one out of three migraine sufferers is actually under a physician's care.[5] Many have resigned themselves to coping on their own.

Fortunately, research may offer new hope to migraine sufferers.
Results of this research have given us new insights into the neurobiological basis of migraine... and new hope for migraine patients.

References:
1. Lance JW. 5-Hydroxytryptamine and its role in migraine. *Eur Neurol.* 1991;31:279-281. **2.** Lance JW. A concept of migraine and the search for the ideal headache drug. *Headache.* January 1990;30:17-23. **3.** Stewart WF, Lipton RB, Celentano DD, Reed ML. Prevalence of migraine headache in the United States: relation to age, income, race, and other sociodemographic factors. *JAMA.* January 1992; 267:64-69. **4.** Prevalence of chronic migraine headaches—United States, 1980-1989. *MMWR.* May 1991;40:331, 337-338. **5.** Data on file, Glaxo Inc.

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- Single-agent efficacy
- Well tolerated†
- No adverse effects on total cholesterol, plasma glucose levels, renal function,‡ or serum electrolytes[3-6]

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Calan® SR

verapamil HCl 180 mg 240 mg

SUSTAINED-RELEASE CAPLETS

For the many faces of mild hypertension

*The recommended starting dose for Calan SR is 180 mg once daily. Dose titration will be required in some patients to achieve blood pressure control. A lower initial starting dosage of 120 mg/day may be warranted in some patients (eg, the elderly, patients of small stature). Dosages above 240 mg daily should be administered in divided doses. Calan SR should be administered with food.

†Constipation, which is easily managed in most patients, is the most commonly reported side effect of Calan SR.

‡Verapamil should be administered cautiously to patients with impaired renal function.

References: 1. Data on file, Searle. 2. Edmonds D, Würth JP, Baumgart P, et al. Twenty-four-hour monitoring of blood pressure during calcium antagonist therapy. In: Fleckenstein A, Laragh SH, eds. *Hypertension—the Next Decade: Verapamil in Focus*. New York, NY: Churchill Livingstone; 1987:94-100. 3. Midtbø KA. Effects of long-term verapamil therapy on serum lipids and other metabolic parameters. *Am J Cardiol*. 1990;66:131-151. 4. Fagher B, Henningsen N, Hulthén L, et al. Antihypertensive and renal effects of enalapril and slow-release verapamil in essential hypertension. *Eur J Clin Pharmacol*. 1990;39(suppl 1):S41-S43. 5. Schmieder RE, Messerli FH, Garavaglia GE, et al. Cardiovascular effects of verapamil in patients with essential hypertension. *Circulation*. 1987;75:1030-1036. 6. Midtbø K, Lauve O, Hals O. No metabolic side effects of long-term treatment with verapamil in hypertension. *Angiology*. 1988;39:1025-1029.

BRIEF SUMMARY

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

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

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

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

2/13/92 • P92CA7196V

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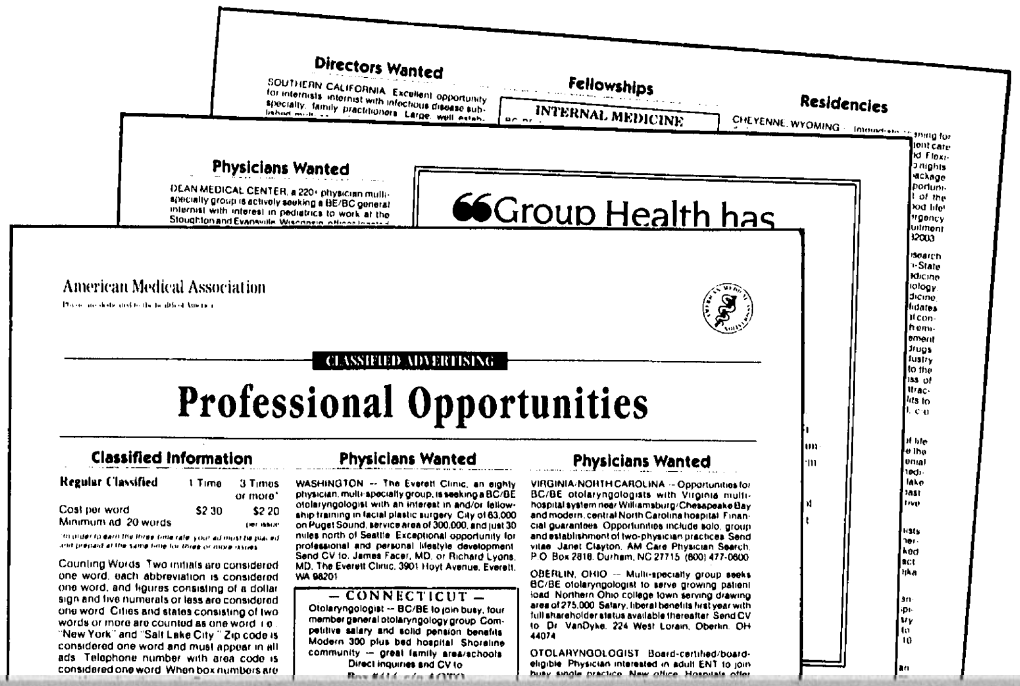

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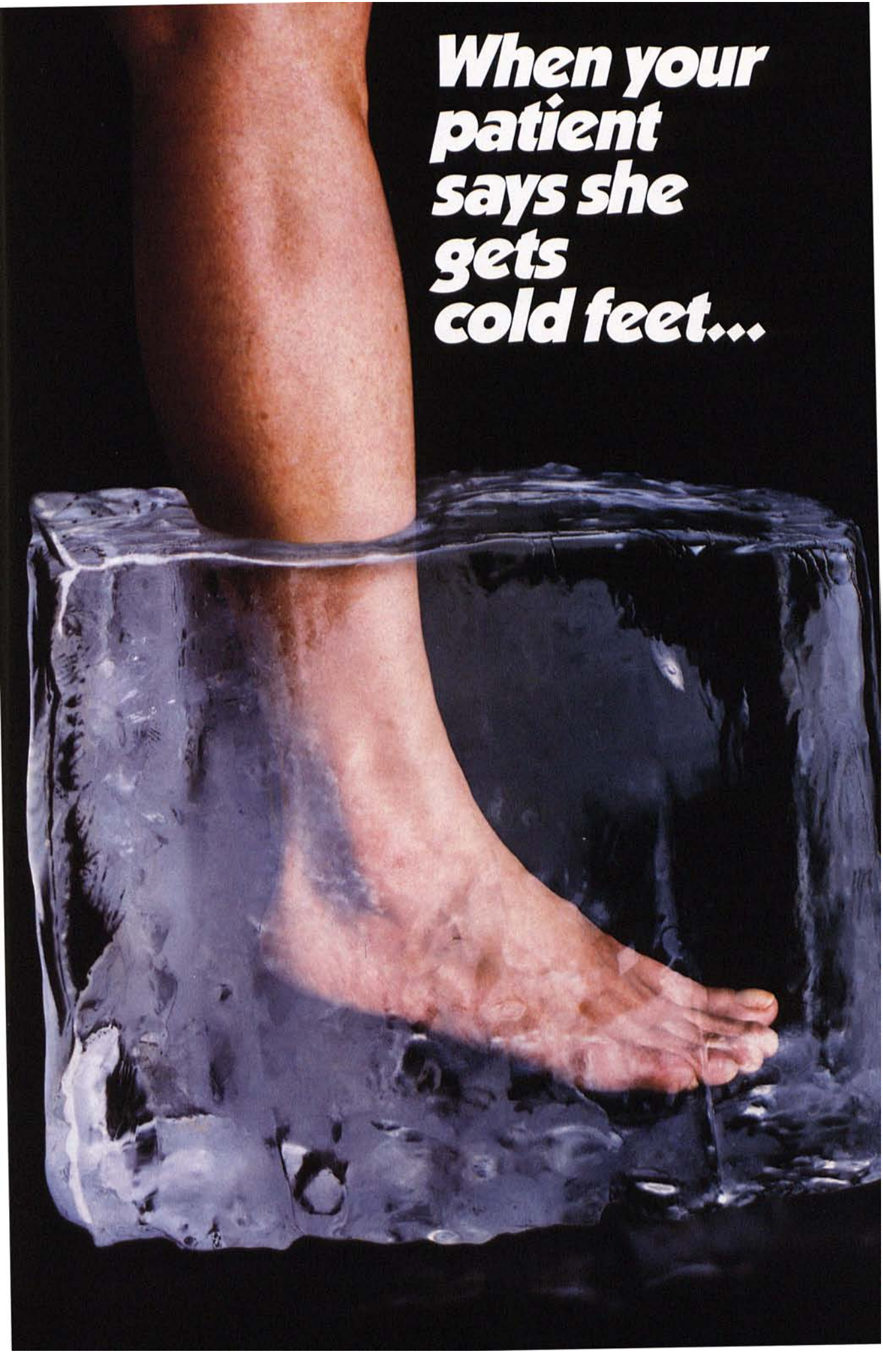

When your patient says she gets cold feet...

References: **1.** Beach KW, Bedford GR, Bergelin RO, et al. Progression of lower-extremity arterial occlusive disease in type II diabetes mellitus. *Diabetes Care.* 1988;11(6):464-472. **2.** Chien S. Determinants of blood viscosity and red cell deformability. Abstracts: 6, International Symposium on Filterability and Red Blood Cell Deformability, Göteborg, Sweden, September 11-13, 1980. **3.** Hanss MF. Filtration methods. Abstracts: 16, International Symposium on Filterability and Red Blood Cell Deformability, Göteborg, Sweden, September 11-13, 1980. **4.** Lowe GDO, Drummond MM, Forbes CD, et al. Blood and plasma viscosity in prediction of venous thrombosis. Abstracts: 77, International Symposium on Filterability and Red Blood Cell Deformability, Göteborg, Sweden, September 11-13, 1980. **5.** Perego MA, Sergio G, Artale F. Haemorrheological aspects of pathophysiology and clinical features of peripheral occlusive arterial disease. *Pharmatherapeutica.* 1983;3(1):91-101. **6.** Störmer B, Kleinschmidt K, Loose D, Kremer K. Rheological changes in the blood of patients with chronic arterial occlusive disease after the administration of vasoactive drugs. *Curr Med Res Opin.* 1977;4:588-595. **7.** Nenci GG, Gresele P, Agnelli G, Ballatori E. Effect of pentoxifylline on platelet aggregation. *Pharmatherapeutica.* 1981;2:532-538. **8.** Seiffge D. Effect of pentoxifylline on red cell aggregation. *IRCS Med Sci.* 1980;8:727. **9.** Johnson WC, Sentissi JM, Baldwin D, Hamilton J, Dion J. Treatment of claudication with pentoxifylline: are benefits related to improvement in viscosity? *J Vasc Surg.* 1987;6(3):211-216. **10.** Schmalzer EA, Chien S. Filterability of subpopulations of leukocytes: effect of pentoxifylline. *Blood.* 1984;64(2):542-546. **11.** Ernst E, Hammerschmidt DE, Bagge U, Matrai A, Dormandy JA. Leukocytes and the risk of ischemic diseases. *JAMA.* 1987;257(17):2318-2324. **12.** Currie M, Simel D, Christenson R, et al. Evidence for pentoxifylline effects on neutrophils *in vivo* by correlations of decreased claudication, coagulation activity, whole blood viscosity, and elastase proteinase inhibitor complexes. Borrowed from the Society for Leukocyte Biology. Marco Island, Fla; 1989. **13.** Ehrly AM. Effects of orally administered pentoxifylline on muscular oxygen pressure in patients with intermittent claudication. *IRCS Med Sci.* 1982;10(5):401-402. **14.** Lindgärde F, Jelnes R, Björkman HJ, et al. Conservative drug treatment in patients with moderately severe chronic occlusive peripheral arterial disease. *Circulation.* 1989;80(6):1549-1556.

Trental® 400 mg Tablets (pentoxifylline)

A brief summary of the Prescribing Information follows.

INDICATIONS AND USAGE:
Trental® (pentoxifylline) is indicated for the treatment of patients with intermittent claudication on the basis of chronic occlusive arterial disease of the limbs. Trental® (pentoxifylline) can improve function and symptoms but is not intended to replace more definitive therapy, such as surgical bypass, or removal of arterial obstructions when treating peripheral vascular disease.

CONTRAINDICATIONS:
Trental® (pentoxifylline) should not be used in patients with recent cerebral and/or retinal hemorrhage, or in patients who have previously exhibited intolerance to this product or methylxanthines such as caffeine, theophylline, and theobromine.

PRECAUTIONS:
General: Patients with chronic occlusive arterial disease of the limbs frequently show other manifestations of arteriosclerotic disease. Trental® (pentoxifylline) has been used safely for treatment of peripheral arterial disease in patients with concurrent coronary artery and cerebrovascular diseases, but there have been occasional reports of angina, hypotension, and arrhythmia. Controlled trials do not show that Trental® (pentoxifylline) causes such adverse effects more often than placebo, but, as it is a methylxanthine derivative, it is possible some individuals will experience such responses. Patients on warfarin should have more frequent monitoring of prothrombin times, while patients with other risk factors complicated by hemorrhage (e.g., recent surgery, peptic ulceration, cerebral and/or retinal bleeding) should have periodic examinations for bleeding including hematocrit and/or hemoglobin.

Drug Interactions: Although a causal relationship has not been established, there have been reports of bleeding and/or prolonged prothrombin time in patients treated with Trental® (pentoxifylline) with and without anticoagulants or platelet aggregation inhibitors. Patients on warfarin should have more frequent monitoring of prothrombin times, while patients with other risk factors complicated by hemorrhage (e.g., recent surgery, peptic ulceration) should have periodic examinations for bleeding including hematocrit and/or hemoglobin. Trental® (pentoxifylline) has been used concurrently with antihypertensive drugs, beta blockers, digitalis, diuretics, antidiabetic agents, and antiarrhythmics without observed problems. Small decreases in blood pressure have been observed in some patients treated with Trental® (pentoxifylline); periodic systemic blood pressure monitoring is recommended for patients receiving concomitant antihypertensive therapy. If indicated, dosage of the antihypertensive agents should be reduced.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term studies of the carcinogenic potential of pentoxifylline were conducted in mice and rats by dietary administration of the drug at doses up to approximately 24 times (570 mg/kg) the maximum recommended human daily dose (MRHD) of 24 mg/kg for 18 months in mice and 18 months in rats with an additional 6 months without drug exposure in the latter. No carcinogenic potential for pentoxifylline was noted in the mouse study. In the rat study, there was a statistically significant increase in benign mammary fibroadenomas in females in the high dose group (24 x MRHD). The relevance of this finding to human use is uncertain since this was only a marginal statistically significant increase for a tumor that is common in aged rats. Pentoxifylline was devoid of mutagenic activity in various strains of Salmonella (Ames test) when tested in the presence and absence of metabolic activation.

Pregnancy: Category C. Teratogenic studies have been performed in rats and rabbits at oral doses up to about 25 and 10 times the maximum recommended human daily dose (MRHD) of 24 mg/kg, respectively. No evidence of fetal malformation was observed. Increased resorption was seen in rats at 25 times MRHD. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Trental® (pentoxifylline) should be used during pregnancy only if clearly needed.

Nursing Mothers: Pentoxifylline and its metabolites are excreted in human milk. Because of the potential for tumorigenicity shown for pentoxifylline in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children below the age of 18 years have not been established.

ADVERSE REACTIONS:
Clinical trials were conducted using either controlled-release Trental® (pentoxifylline) tablets for up to 60 weeks or immediate-release Trental® (pentoxifylline) capsules for up to 24 weeks. Dosage ranges in the tablet studies were 400 mg bid to tid and in the capsule studies, 200-400 mg tid.
The table summarizes the incidence (in percent) of adverse reactions considered drug-related, as well as the numbers of patients who received controlled-release Trental® (pentoxifylline) tablets, immediate-release Trental® (pentoxifylline) capsules, or the corresponding placebos. The incidence of adverse reactions was higher in the capsule studies (where dose-related increases were seen in digestive and nervous system side effects) than in the tablet studies. Studies with the capsule include domestic experience, whereas studies with the controlled-release tablets were conducted outside the U.S. The table indicates that in the tablet studies few patients discontinued because of adverse effects.

INCIDENCE (%) OF SIDE EFFECTS

	Controlled-Release Tablets		Immediate-Release Capsules	
	Commercially Available		Used Only for Controlled Clinical Trials	
	Trental®	Placebo	Trental®	Placebo
(Numbers of Patients at Risk)	(321)	(128)	(177)	(138)
Discontinued for Side Effect	3.1	0	9.6	7.2
CARDIOVASCULAR SYSTEM				
Angina/Chest Pain	0.3	—	1.1	2.2
Arrhythmia/Palpitation	—	—	1.7	0.7
Flushing	—	—	2.3	0.7
DIGESTIVE SYSTEM				
Abdominal Discomfort	—	—	4.0	1.4
Belching/Flatus/Bloating	0.6	—	9.0	3.6
Diarrhea	—	—	3.4	2.9
Dyspepsia	2.8	4.7	9.6	2.9
Nausea	2.2	0.8	28.8	8.7
Vomiting	1.2	—	4.5	0.7
NERVOUS SYSTEM				
Agitation/Nervousness	—	—	1.7	0.7
Dizziness	1.9	3.1	11.9	4.3
Drowsiness	—	—	1.1	5.8
Headache	1.2	1.6	6.2	5.8
Insomnia	—	—	2.3	2.2
Tremor	0.3	0.8	—	—
Blurred Vision	—	—	2.3	1.4

Trental® (pentoxifylline) has been marketed in Europe and elsewhere since 1972. In addition to the above symptoms, the following have been reported spontaneously since marketing or occurred in other clinical trials with an incidence of less than 1%; the causal relationship was uncertain:

Cardiovascular – dyspnea, edema, hypotension.
Digestive – anorexia, cholecystitis, constipation, dry mouth/thirst.
Nervous – anxiety, confusion, depression, seizures.
Respiratory – epistaxis, flu-like symptoms, laryngitis, nasal congestion.
Skin and Appendages – brittle fingernails, pruritus, rash, urticaria, angioedema.
Special Senses – blurred vision, conjunctivitis, earache, scotoma.
Miscellaneous – bad taste, excessive salivation, leukopenia, malaise, sore throat/swollen neck glands, weight change.

A few rare events have been reported spontaneously worldwide since marketing in 1972. Although they occurred under circumstances in which a causal relationship with pentoxifylline could not be established, they are listed to serve as information for physicians: Cardiovascular — angina, arrhythmia, tachycardia, anaphylactoid reactions; Digestive — hepatitis, jaundice, increased liver enzymes; and Hemic and Lymphatic — decreased serum fibrinogen, pancytopenia, aplastic anemia, leukemia, purpura, thrombocytopenia.

OVERDOSAGE:
Overdosage with Trental® (pentoxifylline) has been reported in children and adults. Symptoms appear to be dose-related. A report from a poison control center on 44 patients taking overdoses of enteric-coated pentoxifylline tablets noted that symptoms usually occurred 4-5 hours after ingestion and lasted about 12 hours. The highest amount ingested was 80 mg/kg; flushing, hypotension, convulsions, somnolence, loss of consciousness, fever, and agitation occurred. All patients recovered.
In addition to symptomatic treatment and gastric lavage, special attention must be given to supporting respiration, maintaining systemic blood pressure, and controlling convulsions. Activated charcoal has been used to adsorb pentoxifylline in patients who have overdosed.

DOSAGE AND ADMINISTRATION:
The usual dosage of Trental® (pentoxifylline) in controlled-release tablet form is one tablet (400 mg) three times a day with meals.
While the effect of Trental® (pentoxifylline) may be seen within 2 to 4 weeks, it is recommended that treatment be continued for at least 8 weeks. Efficacy has been demonstrated in double-blind clinical studies of 6 months' duration. Digestive and central nervous system side effects are dose-related. If patients develop these side effects it is recommended that the dosage be lowered to one tablet twice a day (800 mg/day). If side effects persist at this lower dosage, the administration of Trental® (pentoxifylline) should be discontinued.

Trental® REG TM HOECHST AG

Edition 7/91

Hoechst-Roussel Pharmaceuticals Inc.
Somerville, New Jersey 08876-1258

Hoechst

Q73273-192

Patients with intermittent claudication may report other symptoms first:

- Cold feet
- Paresthesia and numbness
- Hair loss and trophic skin changes
- Delayed healing of superficial injuries

You're most likely to hear them from:

- Patients over 50
- Type II diabetics
- Smokers of more than 25 years[1]
- Hypertensives with elevated triglyceride and depressed HDL levels

TRENTAL® increases pain-free walking distance and improves microcirculatory blood flow[2-14*†]:

- Lowers whole blood viscosity
- Increases red cell flexibility
- Lowers red cell aggregation
- Lowers platelet aggregation
- Lowers fibrinogen levels
- Increases white cell flexibility and inhibits neutrophil adhesion and activation

† The clinical significance, if any, of these laboratory findings has not been established.

3 x 3 = Success:

- Patients may improve gradually over 3 months‡
- The usual dosage of TRENTAL® is one 400-mg tablet 3 times a day, with meals
- Therapy must be continued to sustain improvement

Excellent safety profile:

- TRENTAL® has been used concurrently with antihypertensive, beta-blocker, digitalis, diuretic, antidiabetic and antiarrhythmic regimens without observed problems
- Patients on warfarin should have more frequent monitoring of prothrombin time; periodic systemic blood pressure monitoring is recommended for patients receiving concomitant antihypertensive therapy

Trental® 400 mg Tablets t.i.d.

(pentoxifylline)

The only proven-effective agent for intermittent claudication — a symptom of peripheral arterial disease

*TRENTAL® can improve function and symptoms but is not intended to replace more definitive therapy such as surgery.

‡ While the effect of TRENTAL® may be seen within 2 to 4 weeks, it is recommended that treatment be continued for at least 8 weeks.

Please see references and brief summary of prescribing information on following page.

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*

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 ***57,000,000*** *prescriptions written for once-daily verapamil SR‡ over the past 5.5 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 Pharmaceuticals and G.D. Searle & Co.

Please see back for brief summary of prescribing information.

ONCE-DAILY

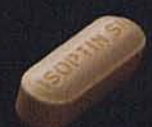
ISOPTIN® SR

(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®

Knoll Pharmaceuticals
A Unit of BASF K&F Corporation
Whippany, New Jersey 07981

BASF (abbr.)

I2073/8-92 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:

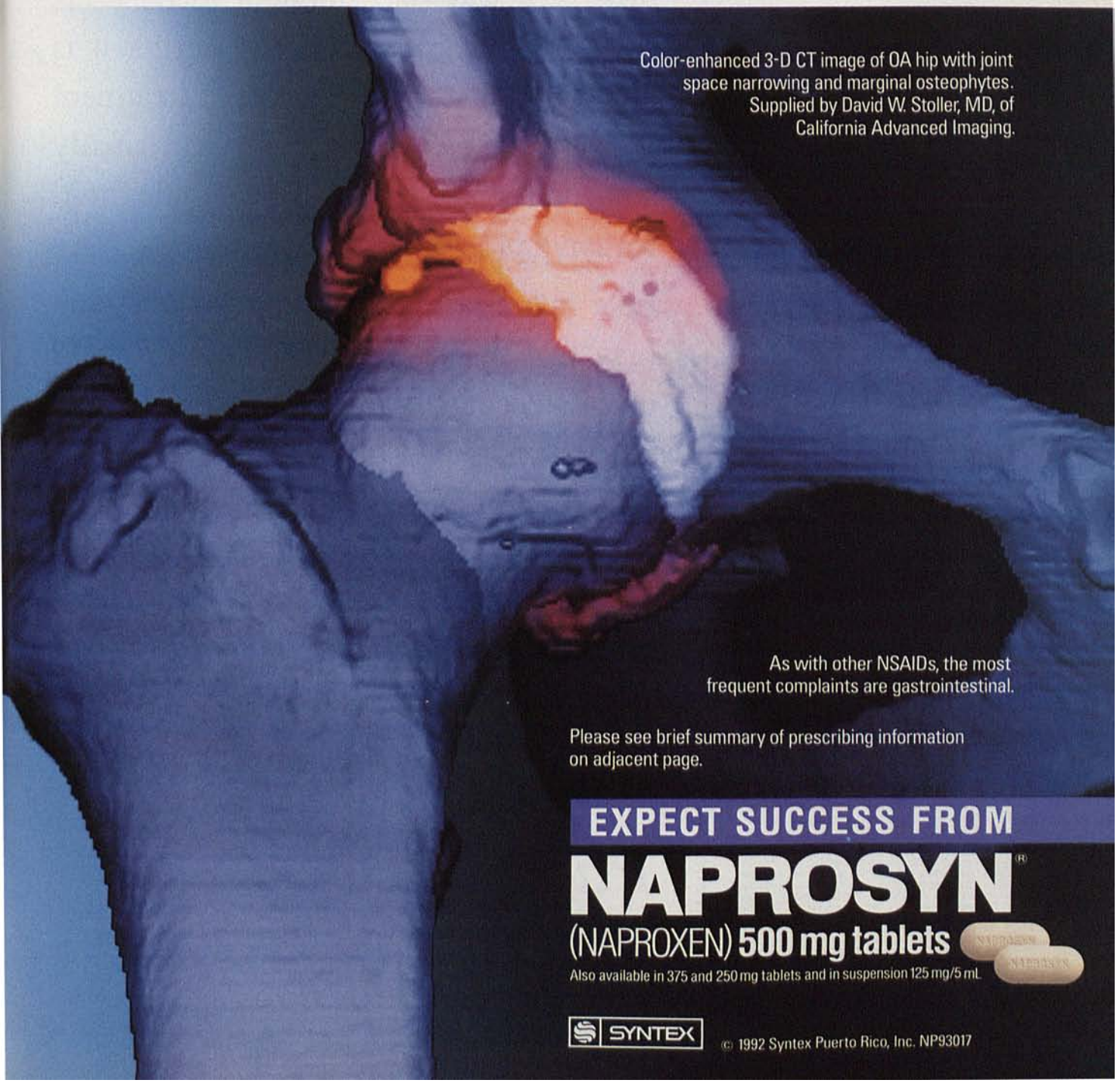
a. 240 mg each morning.
b. 180 mg each morning plus 180 mg each evening, or 240 mg each morning plus 120 mg each evening.
c. 240 mg every twelve hours.

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.

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

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.

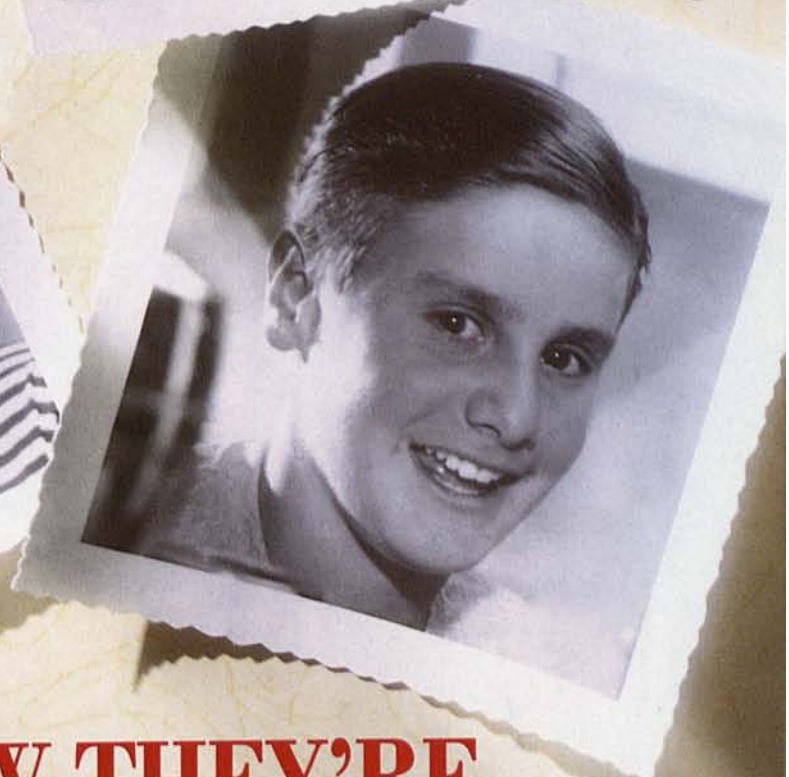
You may be able to offer someone a new lease on life. Or at least, encouragement.

The Paget's Disease Foundation, Inc.

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

THEY WERE CAREFREE...

They were raised in a simpler time, before sugar-free and fat-free. Now hypertension, often with elevated cholesterol and blood sugar, enters the picture...



NOW THEY'RE CONCERNED...

Today's hypertensives with new concerns...

THE CARDURA

*Adapted from the interim (12 months) results of the Treatment of Mild Hypertension Study, a randomized, double-blind, placebo-controlled trial of a nutritional-hygienic regimen along with various drug therapies. All drugs (except acebutolol) were given initially in low doses. If the patient showed a diastolic blood pressure more than 95 mm Hg on three successive follow-up visits, the dosage was doubled. If blood pressure remained elevated, a second drug (chlorthalidone, except for chlorthalidone group, which was given enalapril) was added. Mean diastolic blood pressure was lowered in the various drug groups with median dosages, as follows: doxazosin (2 mg/day), 12.0 mm Hg; enalapril (5 mg/day), 12.2 mm Hg; chlorthalidone (15 mg/day), 13.1 mm Hg; and acebutolol (400 mg/day), 13.7 mm Hg (n=847; $P<0.01$ vs placebo).

†n=128; $P<0.01$ vs placebo. In a pooled analysis of placebo-controlled studies with about 300 predominantly normocholesterolemic patients per treatment group, CARDURA produced a small decrease in total cholesterol (-2.7%) and LDL cholesterol (-4.3%) and a small increase in the HDL/total cholesterol ratio (+4.3%).

‡Adapted from Lehtonen et al[2] (n=77; after 26 weeks: $P<0.001$ compared with week 0 for blood pressure and insulin, $P<0.05$ compared with week 0 for glucose).

GENERATION

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

Choose CARDURA for blood pressure control that doesn't jeopardize blood lipids.

In the Treatment of Mild Hypertension Study, CARDURA lowered diastolic blood pressure (mean 12.0 mm Hg) as effectively as enalapril, chlorthalidone, and acebutolol[1*]

CARDURA lowered blood pressure with a small increase in the HDL/total cholesterol ratio (+2.4%)* in the same study.[1†] The clinical significance of these changes is uncertain. Cholesterol is just one parameter to consider when selecting the best individualized therapy for a given patient

Choose CARDURA for blood pressure control that doesn't compromise blood sugar.

CARDURA controlled diastolic blood pressure without an adverse effect on glucose tolerance or insulin control[2‡]

CARDURA is well tolerated. In placebo-controlled studies, only three common side effects were reported significantly more often than placebo: dizziness, somnolence, and fatigue.[§]

Only 2% of patients discontinued therapy due to adverse effects—the same as with placebo

§ These were generally mild and transient. 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 on last page.

ONCE-A-DAY

CARDURA®

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

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

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

References: 1. 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. **2.** 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.

Pfizer Roerig

Printed in USA January 1992

Triphasil®

Levonorgestrel and ethinyl estradiol tablets—
Triphasic regimen 21- and 28-day regimens

THE OC TO START WITH BECAUSE SHE'LL STAY WITH IT

IN BRIEF:
TRIPHASIL® – 6 brown tablets containing 0.050 mg levonorgestrel with 0.030 mg ethinyl estradiol; 5 white tablets containing 0.075 mg levonorgestrel with 0.040 mg ethinyl estradiol; 10 light-yellow tablets containing 0.125 mg levonorgestrel with 0.030 mg ethinyl estradiol (7 light-green tablets containing inert ingredients are included in the 28-day regimen)—Triphasic regimen.

Indications and Usage – TRIPHASIL® is indicated for the prevention of pregnancy in women who elect to use oral contraceptives (OCs) as a method of contraception.

Contraindications – OCs should not be used in women with any of the following: 1. Thrombophlebitis or thromboembolic disorders. 2. A past history of deep-vein thrombophlebitis or thromboembolic disorders. 3. Cerebral-vascular or coronary-artery disease. 4. Known or suspected carcinoma of the breast. 5. Endometrial carcinoma or other known or suspected estrogen-dependent neoplasia. 6. Undiagnosed abnormal genital bleeding. 7. Cholestatic jaundice of pregnancy or jaundice with prior pill use. 8. Hepatic adenomas or carcinomas. 9. Known or suspected pregnancy.

Warnings

Cigarette smoking increases the risk of serious cardiovascular side effects from oral-contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

Use of OCs is associated with increased risks of serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, gallbladder disease, and hypertension, although risk of serious morbidity/mortality is very small in healthy women without underlying risk factors. Morbidity/mortality risk increases significantly if other risk factors present (i.e. hypertension, hyperlipidemias, obesity, diabetes). Practitioners prescribing OCs should be familiar with the following information relating to these risks. (This information is based principally on data involving OCs with higher doses of estrogen and progestogen than those commonly used today. Effect of long-term use of lower estrogen and progestogen formulations is yet to be determined.)

1. *Thromboembolic Disorders and Other Vascular Problems* – MYOCARDIAL INFARCTION (MI). An increased risk of MI has been attributed to OC use. Risk is primarily in smokers or women with other underlying risk factors for coronary-artery disease (i.e. hypertension, hypercholesterolemia, morbid obesity, diabetes). Relative risk of heart attack for current OC users is estimated to be two to six; risk is very low under the age of 30.

Smoking combined with OC use contributes substantially to incidence of MIs in women in their mid-thirties or older with smoking accounting for majority of excess cases. Mortality rates associated with circulatory disease increase substantially in smokers over the age of 35 and nonsmokers over the age of 40 among OC users.

OCs may compound effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity. In particular, some progestogens decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism. OCs have been shown to increase blood pressure among users (see Warnings). Similar effects on risk factors are associated with increased risk of heart disease. Use OCs with caution in women with cardiovascular disease risk factors.

THROMBOEMBOLISM. Increased risk of thromboembolic and thrombotic disease associated with OC use is well established. In case control studies relative risk of users compared to non-users was 3 for first episode of superficial venous thrombosis, 4 to 11 for deep-vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease. In cohort studies relative risk was somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization. Thromboembolic disease risk due to OCs is not related to length of use and disappears after pill use is stopped.

A 2- to 4-fold increase in relative risk of postoperative thromboembolic complications has been reported with OCs. Relative risk of venous thrombosis in women with predisposing conditions is twice that of women without such conditions. If feasible, discontinue OCs at least 4 weeks prior to and for 2 weeks after elective surgery of a type associated with increased risk of thromboembolism and during and following prolonged immobilization.

Since the immediate postpartum period is associated with an increased thromboembolic risk, start OCs no earlier than 4 to 6 weeks after delivery in women not breast-feeding, or a mid-trimester pregnancy termination.

CEREBROVASCULAR DISEASES. OCs increase relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes); in general, risk is greatest among older (> 35 years), hypertensive women who smoke. Hypertension is a risk factor for users and nonusers, for both types of strokes, while smoking interacts to increase hemorrhagic stroke risk.

DOSE-RELATED RISK OF VASCULAR DISEASE FROM OCS. A positive association has been observed between amount of estrogen and progestogen in OCs and vascular disease risk. A decline in serum high density lipoproteins (HDL) is reported with many progestational agents. Serum HDL decline is associated with increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, net effect depends on balance achieved between doses of estrogen and progestogen and nature and absolute amount of progestogen used. Consider amount of both hormones in the choice of an OC.

The dosage regimen prescribed should contain the least amount of estrogen and progestogen compatible with a low failure rate and individual patient needs. Start new acceptors on preparations containing less than 50 mcg of estrogen.

PERSISTENCE OF RISK OF VASCULAR DISEASE. Two studies have shown persistence of vascular disease risk for ever-users of OCs. In a U.S. study, MI risk after OC discontinuation persists for at least 9 years in women 40-49 years who had used OCs for five or more years; increased risk was not demonstrated in other age groups. In a study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after OCs stopped, although excess risk was very small. Both studies used OC formulations with 50 micrograms or higher of estrogens.

2. *Estimates of Mortality from Contraceptive Use* – A study using data from several sources concluded that with the exception of OC users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is less than that associated with childbirth. The possibility of increased mortality risk with age for OC users is based on data from the 1970s – but reported in 1983. However, current practice involves use of lower estrogen dose formulations combined with careful restriction of OC use to women without the various risk factors listed in this labeling.

Changes in practice and new data suggesting that cardiovascular disease risk with OCs may be less than previously observed prompted the Fertility and Maternal Health Drugs Advisory Committee to review the topic in 1989. The Committee concluded that although cardiovascular-disease risks may be increased with OC use after age 40 in healthy nonsmokers (even with newer low-dose formulations), greater potential health risks are associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if effective, acceptable contraception is not available.

The Committee concluded that the benefits of OC use by healthy nonsmoking women over 40 may outweigh the possible risks. Older women, as all women who take OCs, should use the lowest possible effective dose formulation.

3. *Carcinoma of the Reproductive Organs* – Numerous epidemiological studies have looked at the incidence of breast, endometrial, ovarian and cervical cancer in women using OCs. Overwhelming evidence suggests that OC use is not associated with an increase in risk of developing breast cancer, regardless of the age and parity of first use or with most of the marketed brands and doses. The Cancer and Steroid Hormone (CASH) study also showed no latent effect on breast cancer risk for at least a decade following long-term use. A few studies show a slightly increased relative risk of developing breast cancer, although the methodology of these studies, including differences in examination of users and nonusers, and in age at start of use, has been questioned.

Some studies suggest that OC use is associated with an increased risk of cervical intraepithelial neoplasia in some populations of women. However, controversy continues about the extent to which such findings may be due to differences in sexual behavior and other factors.

In spite of many studies of the relationship between OC use and breast and cervical cancers, a cause and effect relationship has not been established.

4. *Hepatic Neoplasia* – Benign hepatic adenomas are associated with OC use, although incidence is rare in the U.S. Indirect calculations estimate attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after four or more years of use. Rupture of rare, benign, hepatic adenomas may cause death through intra-abdominal hemorrhage.

British studies have shown an increased risk of hepatocellular carcinoma in long-term (> 8 years) OC users; these cancers are extremely rare in the U.S. and attributable risk (excess incidence) of liver cancers in OC users approaches less than one per million users.

5. *Ocular Lesions* – There are clinical case reports of retinal thrombosis with OC use. Discontinue OCs if there is unexplained partial or complete loss of vision, onset of proptosis or diplopia, papilledema, or retinal vascular lesions; undertake appropriate diagnostic and therapeutic measures immediately.

6. *Oral-Contraceptive Use Before or During Early Pregnancy* – Extensive epidemiological studies revealed no increased risk of birth defects when OCs used prior to pregnancy. Studies do not suggest a teratogenic effect, particularly insofar as cardiac anomalies and limb reduction defects are concerned, when taken inadvertently during early pregnancy. OC-induced withdrawal bleeding should not be used as a pregnancy test. Do not use OCs during pregnancy to treat threatened or habitual abortion. Rule out pregnancy if two consecutive periods missed before continuing OC use. If patient has not adhered to prescribed schedule, consider pregnancy at time of first missed period. Discontinue OC if pregnancy confirmed.

7. *Gallbladder Disease* – Earlier studies reported an increased lifetime relative risk of gallbladder surgery in users of OCs and estrogens; more recent studies show that the relative risk of developing gallbladder disease among OC users may be minimal, which may be related to use of formulations with lower hormonal estrogen and progestogen doses.

8. *Carbohydrate and Lipid Metabolic Effects* – OCs cause glucose intolerance in a significant percentage of users. OCs with greater than 75 µg of estrogen cause hyperinsulinism; lower estrogen doses cause less glucose intolerance. Progestogens increase insulin secretion and create insulin resistance (effect varies with different agents). Observe prediabetic and diabetic women carefully while taking OCs. In non-diabetic women, OCs have no apparent effect on fasting blood glucose.

A small proportion of women will have persistent hypertriglyceridemia while on OCs. Changes in serum triglycerides and lipoprotein levels have been reported in OC users (see Warnings).

9. *Elevated Blood Pressure* – Increase in blood pressure has been reported in women on OCs; increase is more likely in older OC users and with continued use. Data show that incidence of hypertension increases with increasing quantities of progestogens.

Encourage women with history of hypertension or hypertension-related diseases, or renal disease to use another contraceptive method. Monitor hypertensive women electing to use OCs closely; discontinue OC if significant blood pressure elevation occurs. For most women, elevated blood pressure returns to normal after OC stopped. No difference in occurrence of hypertension among ever- and never-users exists.

10. *Headache* – Discontinue OC and evaluate cause at onset or exacerbation of migraine, or if new pattern of headache (i.e. recurrent, persistent, severe) develops.

11. *Bleeding Irregularities* – Breakthrough bleeding and spotting sometimes occur, especially during first 3 months of use. Type and dose of progestogen may be important. Consider non-hormonal causes and take adequate diagnostic measures to rule out malignancy or pregnancy in event of breakthrough bleeding, as with any abnormal vaginal bleeding. If pathology excluded, time or a formulation change may solve the problem. In the event of amenorrhea, rule out pregnancy. Some women encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was pre-existent.

Precautions

1. *Physical Examination and Follow Up* – A complete medical history and physical examination should be taken prior to initiation or reinstitution of OCs and at least annually during use. Physical exams should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, conduct appropriate diagnostic measures to rule out malignancy. Monitor women with strong family history of breast cancer or who have breast nodules with particular care. 2. *Lipid Disorders* – Follow women being treated for hyperlipidemias closely if they elect to use OCs. Some progestogens may elevate LDL levels and may render control of hyperlipidemias more difficult. (See Warnings) 3. *Liver Function* – Discontinue OC if jaundice develops. Steroid hormones may be poorly metabolized in patients with impaired liver function. 4. *Fluid Retention* – OCs may cause some degree of fluid retention. Prescribe with caution, and only with careful monitoring, in patients with conditions possibly aggravated by fluid retention. 5. *Emotional Disorders* – If significant depression occurs stop medication and use alternate contraceptive method in attempts to determine if symptom is drug related. Observe carefully those with history of depression and stop drug if depression recurs to serious degree. 6. *Contact Lenses* – Contact-lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist. 7. *Drug Interactions* – Reduced efficacy and increased incidence of breakthrough bleeding and menstrual irregularities are associated with concomitant rifampin use. A similar association, though less marked, is suggested with barbiturates, phenylbutazone, phenytoin sodium, and possibly with griseofulvin, ampicillin and tetracyclines. 8. *Interactions with Laboratory Tests* – Certain endocrine- and liver-function tests and blood components may be affected by OCs: a. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. b. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. c. Other binding proteins may be elevated in serum. d. Sex-binding globulins are increased and result in elevated levels of total circulating sex steroids and corticoids; free or biologically active levels remain unchanged. e. Triglycerides may be increased. f. Glucose tolerance may be decreased. g. Serum folate levels may be depressed by OCs. This may be of clinical significance if woman becomes pregnant shortly after stopping OC. 9. *Carcinogenesis* – See Warnings section. 10. *Pregnancy* – Pregnancy Category X. See Contraindications and Warnings. 11. *Nursing Mothers* – Small amounts of OC steroids have been identified in milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, OCs given in postpartum period may interfere with lactation by decreasing breast milk quantity and quality. If possible, advise nursing mother to use other forms of contraception, not OCs, until child is completely weaned.

Information for the Patient – See Patient Package Labeling.

Adverse Reactions – An increased risk of the following serious adverse reactions has been associated with OC use (see Warnings): thrombophlebitis; arterial thromboembolism; pulmonary embolism; myocardial infarction; cerebral hemorrhage; cerebral thrombosis; hypertension; gallbladder disease; hepatic adenomas or benign liver tumors.

There is evidence of an association between the following conditions and OC use, although additional confirmatory studies are needed: mesenteric thrombosis; retinal thrombosis.

The following adverse reactions have been reported in patients on OCs and are believed to be drug-related: nausea; vomiting; gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding; spotting; change in menstrual flow; amenorrhea; temporary infertility after treatment discontinued; edema; melasma which may persist; breast changes: tenderness, enlargement, secretion; change in weight (increase or decrease); change in cervical erosion and secretion; diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature (steepening); intolerance to contact lenses.

The following adverse reactions have been reported in OC users and the association is neither confirmed nor refuted: congenital anomalies; premenstrual syndrome; cataracts; optic neuritis; changes in appetite; cystitis-like syndrome; headache; nervousness; dizziness; hirsutism; loss of scalp hair; erythema multiforme; erythema nodosum; hemorrhagic eruption; vaginitis; porphyria; impaired renal function; hemolytic uremic syndrome; Budd-Chiari syndrome; acne; changes in libido; colitis; sickle-cell disease; cerebral-vascular disease with mitral valve prolapse; lupus-like syndromes.

Overdosage – Serious ill effects have not been reported following acute ingestion of large doses of OCs by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

Noncontraceptive Health Benefits – The following noncontraceptive health benefits related to OC use are supported by epidemiological studies that largely utilized OC formulations containing doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg of mestranol. *Effects on menses*: increased menstrual cycle regularity; decreased blood loss and decreased incidence of iron-deficiency anemia; decreased incidence of dysmenorrhea. *Effects related to inhibition of ovulation*: decreased incidence of functional ovarian cysts; decreased incidence of ectopic pregnancies. *Effects from long-term use*: decreased incidence of fibroadenomas and fibrocystic disease of the breast; decreased incidence of acute pelvic inflammatory disease; decreased incidence of endometrial cancer; decreased incidence of ovarian cancer.

Dosage and Administration – For maximum contraceptive effectiveness, take TRIPHASIL® (levonorgestrel and ethinyl estradiol tablets – triphasic regimen 21- and 28-day regimens) exactly as directed and at intervals not over 24 hours.

(If TRIPHASIL® is first taken later than first day of first menstrual cycle of medication or postpartum, contraceptive reliance should not be placed on it until after the first 7 consecutive days of use. Possibility of ovulation and conception prior to initiation of medication should be considered.) For full details on dosage and administration see prescribing information in package insert.

Worldwide Leadership in Female Healthcare™

WYETH-AYERST LABORATORIES
Philadelphia, PA 19101

11/15/90 CI 3421-6
4/9/90 CI 3428-6

70280

Triphasil®

Levonorgestrel - and ethinyl estradiol tablets-
Triphasic regimen 21- and 28-day regimens

THE OC TO START WITH BECAUSE SHE'LL STAY WITH IT

▼

Simple, easy-to-use
Day 1 Start

▼

Patient acceptance
proven over time*

* Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives. See prescribing information.

See brief summary on adjacent page.

Worldwide Leadership in Female Healthcare™

WYETH-AYERST LABORATORIES
Philadelphia, PA 19101

In upper and lower respiratory tract infections, BIAXIN...

Spans the Spectrum o
and Erythromycin

- The key respiratory spectrum of the beta-lactams, plus the atypical spectrum of erythromycin... *H. influenzae, S. pyogenes, M. catarrhalis* and *M. pneumoniae*[1-4]
- Excellent tissue penetration without sacrificing therapeutic serum levels[1,5]

† Due to susceptible strains of indicated organisms.
‡ Clinical success rate–clinical cure or improvement within 4–6 days post-treatment.

Please see following page for brief summary of Prescribing Information.

the Beta-lactams

- Excellent clinical success rates in community-acquired pneumonia, acute exacerbation of chronic bronchitis, pharyngitis, tonsillitis, and acute maxillary sinusitis*†[1,6,7]
- Tolerability comparable to beta-lactams;[1,7] convenient BID dosing

BIAXIN™

clarithromycin

250 mg and 500 mg Tablets

SPANS THE SPECTRUM

BIAXIN™

(Clarithromycin)

Filmtab® Tablets

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE
BIAXIN (Clarithromycin) is indicated for the treatment of mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below:
Upper Respiratory Tract Infections
Pharyngitis/Tonsilitis due to *Streptococcus pyogenes*
Acute maxillary sinusitis due to *Streptococcus pneumoniae*
Lower Respiratory Tract Infections
Acute bacterial exacerbation of chronic bronchitis due to *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae*
Pneumonia due to *Mycoplasma pneumoniae* or *Streptococcus pneumoniae*
Uncomplicated Skin and Skin Structure Infections due to *Staphylococcus aureus* or *Streptococcus pyogenes*. Abscesses usually require surgical drainage.
CONTRAINDICATIONS
Clarithromycin is contraindicated in patients with a known hypersensitivity to clarithromycin, erythromycin or any of the macrolide antibiotics.
WARNINGS
CLARITHROMYCIN SHOULD NOT BE USED IN PREGNANT WOMEN EXCEPT IN CLINICAL CIRCUMSTANCES WHERE NO ALTERNATIVE THERAPY IS APPROPRIATE. IF PREGNANCY OCCURS WHILE TAKING THIS DRUG, THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO THE FETUS. CLARITHROMYCIN HAS DEMONSTRATED ADVERSE EFFECTS ON PREGNANCY OUTCOME AND/OR EMBRYO-FETAL DEVELOPMENT IN MONKEYS, RATS, MICE, AND RABBITS AT DOSES THAT PRODUCED PLASMA LEVELS 2 TO 17 TIMES THE SERUM LEVELS ACHIEVED IN HUMANS TREATED AT THE MAXIMUM RECOMMENDED HUMAN DOSES. (SEE PREGNANCY.)

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

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

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

PRECAUTIONS
General: Clarithromycin is principally excreted via the liver and kidney. Clarithromycin may be administered without dosage adjustment to patients with hepatic impairment and normal renal function. However, in the presence of severe renal impairment with or without coexisting hepatic impairment, decreased dosage intervals may be appropriate.

Drug Interactions: Clarithromycin use in patients who are receiving theophylline may be associated with an increase of serum theophylline concentrations. Monitoring of serum theophylline concentrations should be considered for patients receiving high doses of theophylline or with baseline concentrations in the upper therapeutic range. In two studies in which theophylline was administered with clarithromycin (a theophylline sustained released formulation was dosed at either 6.5 mg/kg or 12 mg/kg together with 250 mg or 500 mg q 12 h clarithromycin), the steady-state levels of Cmax, Cmin, and the area under the serum concentration time curve (AUC) increased about 20%.

Single-dose administration of clarithromycin has been shown to result in increased concentrations of carbamazepine. Blood level monitoring of carbamazepine may be considered.

The following drug interactions have not been reported in clinical trials with clarithromycin; however, they have been observed with erythromycin products:

Concomitant administration of erythromycin and digoxin has been reported to result in elevated digoxin levels.

There have been reports of increased anticoagulant effects when erythromycin and oral anticoagulants were used concomitantly.

Concurrent use of erythromycin and ergotamine or dihydroergotamine has been associated in some patients with acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.

Erythromycin has been reported to decrease the clearance of triazolam and thus may increase the pharmacologic effect of triazolam.

The use of erythromycin in patients concurrently taking drugs metabolized by the cytochrome P450 system may be associated with elevations in serum levels of these other drugs. There have been reports of interactions of erythromycin with carbamazepine, cyclosporine, hexobarbital, and phenytoin. Serum concentrations of drugs metabolized by the cytochrome P450 system should be monitored closely in patients concurrently receiving erythromycin.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The following *in vitro* mutagenicity tests have been conducted with clarithromycin:

Salmonella/Mammalian Microsome Test
Bacterial Induced Mutation Frequency Test
In Vitro Chromosome Aberration Test
Rat Hepatocyte DNA Synthesis Assay
Mouse Lymphoma Assay
Mouse Dominant Lethal Study
Mouse Micronucleous Test

All tests had negative results except the *In Vitro* Chromosome Abberation Test which was weakly positive in one test and negative in another.

In addition, a Bacterial Reverse-Mutation Test (Ames Test) has been performed on clarithromycin metabolites with negative results.

Fertility and reproduction studies have shown that daily doses of 150-160 mg/kg/day to male and female rats caused no adverse effects on the estrous cycle, fertility, parturition, or number and viability of offspring. Plasma levels in rats after 150 mg/kg/day were 2 times the human serum levels.

In the 150 mg/kg/day monkey studies, plasma levels were 3 times the human serum levels. When given orally after 150mg/kg/day, clarithromycin was shown to produce embryonic loss in monkeys. This affect has been attributed to marked maternal toxicity of the drug at this high dose.

In rabbits *in utero* fetal loss occurred at an intravenous dose of 33 mg/sq m, which is 17 times less than the maximum proposed human oral daily dose of 618 mg/sq m.

Long-term studies in animals have not been performed to evaluate carcinogenic potential.

Pregnancy: Teratogenic Effects. Pregnancy Category C. Four teratogenicity studies in rats (three with oral doses and one with intravenous doses up to 160 mg/kg/day administered during the period of major organogenesis) and two in rabbits (at oral doses up to 125 mg/kg/day or intravenous doses of 30 mg/kg/day administered during gestation days 6 to 18) failed to demonstrate any teratogenicity from clarithromycin. Two additional oral studies in a different rat strain at similar doses and similar conditions demonstrated a low incidence of cardiovascular anomalies at doses of 150 mg/kg/day administered during gestation days 6 to 15. Plasma levels after 150 mg/kg/day were 2 times the human serum levels. Four studies in mice revealed a variable incidence of cleft palate following oral doses of 1000 mg/kg/day during gestation days 6 to 15. Cleft palate was also seen at 500 mg/kg/day. The 1000 mg/kg/day exposure resulted in plasma levels 17 times the human serum levels. In monkeys, an oral dose of 70 mg/kg/day produced fetal growth retardation at plasma levels that were 2 times the human serum levels.

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

Nursing Mothers: It is not known whether clarithromycin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when clarithromycin is administered to a nursing woman. It is known that clarithromycin is excreted in the milk of lactating animals and that other drugs of this class are excreted in human milk.

Pediatric Use: Safety and effectiveness of clarithromycin in children under 12 years of age have not been established.

Geriatric Use: In a steady-state study in which healthy elderly subjects (age 65 to 81 years old) were given 500 mg every 12 hours, the maximum concentrations of clarithromycin and 14-OH clarithromycin were increased. The AUC was also increased. These changes in pharmacokinetics parallel known age-related decreases in renal function. In clinical trials, elderly patients did not have an increased incidence of adverse events when compared to younger patients. Dosage adjustment should be considered in the elderly patients with severe renal impairment.

ADVERSE REACTIONS
The majority of side effects observed in clinical trials were of a mild and transient nature. Fewer than 3% of patients discontinued therapy because of drug-related side effects.

The most frequently reported events, whether drug-related or not were diarrhea (3%), nausea (3%), abnormal taste (3%), dyspepsia (2%), abdominal pain/discomfort (2%), and headache (2%). Most of these events were described as mild or moderate in severity. Of the reported adverse events, only 1% were described as severe.

In studies of pneumonia comparing clarithromycin to erythromycin base or erythromycin stearate, there were fewer adverse events involving the digestive system in clarithromycin-treated patients compared to erythromycin-treated patients (13% vs. 32%, $p < 0.01$). Twenty percent of erythromycin-treated patients discontinued therapy due to adverse events compared to 4% of clarithromycin-treated patients.

The following adverse events have been reported with erythromycin products but not in clinical trials of clarithromycin.

Rarely, erythromycin has been associated with ventricular arrhythmias, including ventricular tachycardia and torsades de pointes, in individuals with prolonged QT intervals.

Changes in Laboratory Values: Changes in laboratory values with possible clinical significance were as follows:

Hepatic - Elevated SGPT (ALT) < 1%, SGOT (AST) < 1%, GGT < 1%, alkaline phosphate <1%, LDH < 1%, and total bilirubin < 1%.

Hematologic - Decreased WBC < 1%, and elevated prothrombin time 1%. Renal - Elevated BUN 4%, and elevated serum creatinine <1%.

Revised April 1992

References: 1. Dela on file, Abbott Laboratories. 2. Kennedy DW, Shikhana AH, Sinusitis. In: Rakel RE, ed. *Conn's Current Therapy 1990*. Philadelphia: WB Saunders, 1990:187-189. 3. Gantz NM. Outpatient management of bacterial lower respiratory tract infections. *Drug Therapy*. March 1990:51-58. 4. Raff MJ, Ramirez JA. Lower respiratory tract infections. *A brief review. Infections in Medicine*. August 1991:45-48,58. 5. Fraschini F, Scaglione F, Pintucci G, Maccarinelli G, Dugnani S, Demartini G. The diffusion of clarithromycin and roxithromycin into nasal mucosa, tonsil and lung in humans. *J Antimicrob Chemother* 1991;27 (suppl A):61-65. 6. Gupta S, Northcott VJ, Prokocimer P, Craft JC. Comparative efficacy and safety of clarithromycin and ampicillin in the treatment of acute bacterial exacerbations of chronic bronchitis (Abstract). Presented at the 30th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, October 1990, Atlanta, Ga. 7. Karma P, Pukander J, Penttila M, et al. The comparative efficacy and safety of clarithromycin and amoxycillin in the treatment of outpatients with acute maxillary sinusitis. *J Antimicrob Chemother*. 1991;27 (suppl A):83-90.

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2048641R

Narcotic efficacy. No narcotic drawbacks.

An effective substitute for injectable narcotics

TORADOL® IM
INJECTION 15, 30, 60 MG
(KETOROLAC TROMETHAMINE)

An effective substitute for oral narcotic combinations

TORADOL® ORAL
10 MG TABLETS
(KETOROLAC TROMETHAMINE)

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

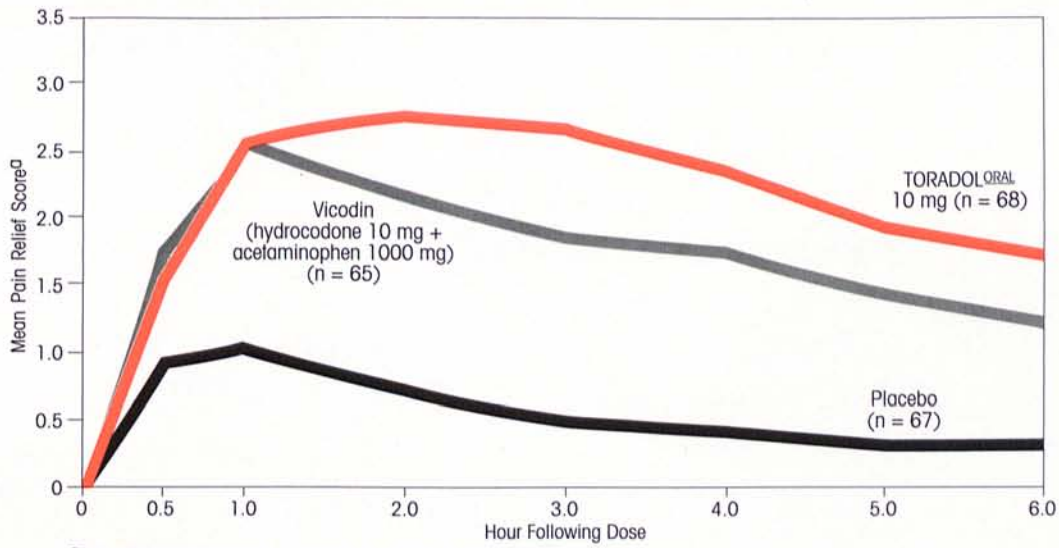
TORADOL® ORAL
10 MG TABLETS
(KETOROLAC TROMETHAMINE)

Efficacy comparable to oral narcotic combinations

- TORADOL ORAL 10 mg as effective as acetaminophen 600 mg + codeine 60 mg and longer acting than Vicodin (two regular tablets)[1]
- An analgesic NSAID for limited-duration use prn for the majority of acute pain conditions
- A substitute for oral narcotic combinations

Efficacy comparison vs Vicodin[1]

Single-dose comparison of TORADOL ORAL vs Vicodin (two regular tablets) and placebo in a double-blind, randomized, parallel clinical study in patients with postoperative pain following dental impaction surgery.[1]



[a]Pain relief rated: 0 = none, 1 = a little, 2 = some, 3 = a lot, and 4 = complete

In this study, patients treated with a single dose of 10 mg of TORADOL ORAL experienced longer duration of action as compared to patients treated with the equivalent of two regular Vicodin tablets[1]

Patients receiving TORADOL ORAL reported significantly fewer GI ($P < .001$) and CNS ($P = .02$) adverse events than those patients receiving Vicodin*[1]

* The most frequently reported side effects are gastrointestinal (dyspepsia, nausea, and GI pain) and CNS (headache). The most serious risks associated with TORADOL are gastrointestinal ulcerations, bleeding, and perforation; renal events ranging from interstitial nephritis to acute renal failure, especially in patients with preexisting kidney problems; hemorrhage; and hypersensitivity reactions.

See "Warnings," "Precautions," and "Adverse Reactions" sections of prescribing information.

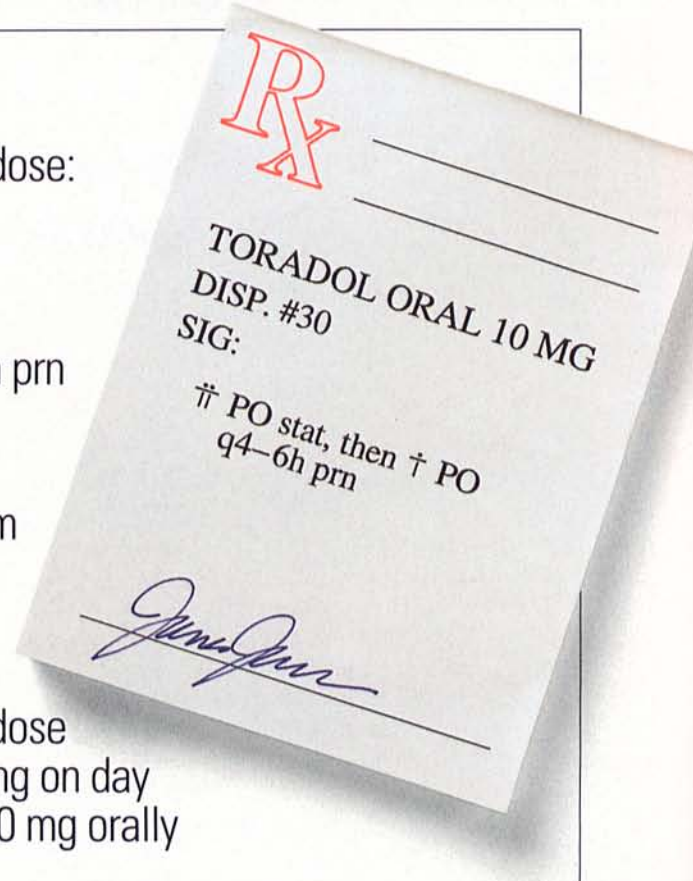
Please see brief summary of prescribing information on last pages of this advertisement.

Narcotic efficacy. No narcotic drawbacks.

Nonopiate. Nonaddictive. Nonscheduled.

Dosing: TORADOL ORAL

- Recommended loading dose: two 10 mg tablets stat
- Maintenance dose: One 10 mg tablet q4–6h prn for limited-duration use
- Recommended maximum daily oral dose: 40 mg
- IM to ORAL transitional dosing: Total combined dose should not exceed 120 mg on day of transition, including 40 mg orally



The only analgesic NSAID available in both IM and oral forms.

TORADOL® IM INJECTION 15, 30, 60 MG ORAL TABLETS 10 MG

(KETOROLAC TROMETHAMINE)

Redefining acute pain management

Reference: 1. Data on file, Syntex Laboratories, Inc., Document #PO93019-3.

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

SYNTEX | Roche

BRIEF SUMMARY

DESCRIPTION

TORADOL is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs (NSAIDs). TORADOL IM is available for intramuscular (IM) administration as: 15 mg in 1 mL (1.5%), 30 mg in 1 mL (3%), or 60 mg in 2 mL (3%) of ketorolac tromethamine in sterile solution. The 15 mg/mL solution contains 10% (w/v) alcohol, USP, and 6.68 mg of sodium chloride in sterile water. The 30 mg/mL solution contains 10% (w/v) alcohol, USP, and 4.35 mg sodium chloride in sterile water. The pH is adjusted with sodium hydroxide or hydrochloric acid and the solutions are packaged with nitrogen. The sterile solutions are clear and slightly yellow in color. TORADOL ORAL is available as round, white, film-coated, red-printed tablets. Each tablet contains 10 mg ketorolac tromethamine, the active ingredient, with lactose, magnesium stearate, and microcrystalline cellulose. The white film-coating contains hydroxypropyl methylcellulose, polyethylene glycol, and titanium dioxide. The tablets are printed with red ink which includes FD&C Red #40 Aluminum lake as the colorant.

INDICATIONS AND USAGE

TORADOL IM is indicated for the short-term management (up to 5 days) of pain (see "Clinical Studies" in CLINICAL PHARMACOLOGY section of full prescribing information). TORADOL IM is not recommended for longer use (more than 5 days) because of the possibility of increased frequency and severity of adverse reactions associated with the recommended doses (see WARNINGS, DOSAGE AND ADMINISTRATION section of full prescribing information and ADVERSE REACTIONS). TORADOL IM is not recommended as a pre-operative medication for support of anesthesia, because it inhibits platelet aggregation and may prolong bleeding time (see PRECAUTIONS — Hematologic Effects) and because it possesses no sedative or anxiolytic properties. TORADOL® IM is not recommended in obstetric analgesia because it has not been adequately studied for such use and because of the known effects of drugs that inhibit prostaglandin synthesis on uterine contraction and fetal circulation. TORADOL IM has been used concomitantly with morphine and meperidine without apparent adverse effects. TORADOL ORAL is indicated for limited duration prn use in the management of pain (see WARNINGS, ADVERSE REACTIONS and CLINICAL PHARMACOLOGY - Clinical Studies Sections of full prescribing information for details about relative risks associated with TORADOL ORAL). TORADOL ORAL is not recommended for long-term use in patients with chronic painful conditions. TORADOL IM and ORAL are not recommended for concurrent use with other nonsteroidal anti-inflammatory drugs (NSAIDs) because of the potential for additive side effects. The protein-binding of ketorolac is affected by aspirin (see PRECAUTIONS) but not by acetaminophen, ibuprofen, naproxen or piroxicam; studies with other nonsteroidals have not been performed.

CONTRAINDICATIONS

TORADOL should not be used in patients with previously demonstrated hypersensitivity to ketorolac tromethamine, or in individuals with the complete or partial syndrome of nasal polyps, angioedema, bronchospastic reactivity (e.g., asthma) or other allergic manifestations to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). Severe anaphylactic-like reactions to TORADOL have been reported in such patients. Therefore, before starting therapy, careful questioning of patients for such things as asthma, nasal polyps, urticaria, and hypotension associated with nonsteroidal anti-inflammatory drugs is important. In addition, if such symptoms occur during therapy, treatment should be discontinued.

WARNINGS

The most serious risks associated with TORADOL are: ***gastrointestinal*** ulcerations, bleeding and perforation (see PRECAUTIONS); ***renal*** events ranging from interstitial nephritis to acute renal failure (see PRECAUTIONS), especially in patients with pre-existing kidney problems; ***hemorrhage***, especially in patients where strict hemostasis is critical (see PRECAUTIONS); ***hypersensitivity reactions*** such as anaphylaxis, bronchospasm, vascular collapse, urticaria, angioedema, Stevens-Johnson syndrome and vesicular bullous rash. Anaphylactoid reactions may occur in patients with a history of hypersensitivity to aspirin, other nonsteroidal anti-inflammatory drugs, or TORADOL. They may, however, also occur in patients without a known previous exposure or hypersensitivity to these agents. Both types of reactions may be fatal. The use of TORADOL IM at recommended doses for more than 5 days is associated with an increased frequency and severity of adverse events. The use of TORADOL ORAL 10 mg on a long-term basis is associated with more GI tract adverse effects than aspirin 650 mg qid (see CLINICAL PHARMACOLOGY — Clinical Studies section of full prescribing information). Long-term treatment is not recommended (see INDICATIONS AND USAGE section of full prescribing information). High oral doses (e.g., 80 or 120 mg/day) are not recommended because risks of serious adverse events are greater with daily doses exceeding the recommended 40 mg oral per day (see ADVERSE REACTIONS).

PRECAUTIONS

Physicians should be alert to the pharmacologic similarity of TORADOL to other nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit cyclo-oxygenase.

General Precautions

Risk of Gastrointestinal Ulcerations, Bleeding and Perforation: Serious gastrointestinal toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Studies to date with NSAIDs 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 other factors have been associated with increased risk. 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 this population. Postmarketing experience with TORADOL IM suggests that there may be a greater risk of gastrointestinal ulcerations, bleeding and perforation in the elderly. Studies so far are inconclusive concerning the relative risk of various nonsteroidal anti-inflammatory drugs (NSAIDs) in causing such reactions. High doses of any such agent probably carry a greater risk of these reactions, although this is rarely established in controlled clinical trials. In considering the intramuscular use of relatively large doses (within the recommended dosage range), or treatment with TORADOL IM for a duration longer than 5 days, sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity. The risks of gastrointestinal side effects associated with long-term use of TORADOL ORAL are described under CLINICAL PHARMACOLOGY — Clinical Studies (Long-Term Use of TORADOL) section of full prescribing information.

Impaired Renal or Hepatic Function: As with other nonsteroidal anti-inflammatory drugs (NSAIDs), TORADOL should be used with caution in patients with impaired renal or hepatic function, or a history of kidney or liver disease.

Renal Effects: As with other nonsteroidal anti-inflammatory drugs (NSAIDs), administration of ketorolac tromethamine to animals resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of hematuria, proteinuria, glomerular nephritis, interstitial nephritis, renal papillary necrosis, nephrotic syndrome, and acute renal failure. Another, equally important, renal toxicity has been seen in patients with conditions leading to a reduction in blood volume and/or renal blood flow, where renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug (NSAID) may cause a dose-dependent reduction in renal prostaglandin formation and may precipitate acute renal failure. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. TORADOL and its metabolites are eliminated primarily by the kidneys which, in patients with reduced creatinine clearance, will result in diminished clearance of the drug (see CLINICAL PHARMACOLOGY section of full prescribing information). Therefore, TORADOL should be used with caution in patients with impaired renal function (see WARNINGS, and DOSAGE AND ADMINISTRATION section of full prescribing information) and such patients should be followed closely.

Fluid Retention and Edema: As with other nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit prostaglandin biosynthesis, fluid retention, edema, retention of NaCl, oliguria, elevations of serum urea nitrogen and creatinine have been reported in clinical trials with TORADOL. Therefore, TORADOL should be used with caution in patients with acute renal failure, cardiac decompensation, hypertension, or similar conditions.

Hepatic Effects: As with other nonsteroidal anti-inflammatory drugs (NSAIDs), treatment with TORADOL may cause elevations of liver enzymes, and in patients with pre-existing liver dysfunction, it may lead to the development of a more severe hepatic reaction. The ALT (SGPT) test is probably the most sensitive indicator of liver injury. In patients with symptoms and signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred as a result of TORADOL therapy, the administration of the drug should be discontinued.

Hematologic Effects: TORADOL inhibits platelet aggregation and may prolong bleeding time. Unlike aspirin, the inhibition of platelet function by TORADOL disappears within 24 to 48 hours after the drug is discontinued. TORADOL does not appear to affect platelet count, prothrombin time (PT) or partial thromboplastin time (PTT). In controlled clinical studies where TORADOL was administered intramuscularly or intravenously postoperatively, the incidence of clinically significant postoperative bleeding was 0.4% for TORADOL compared to 0.2% in the control groups receiving narcotic analgesics. Because prostaglandins play an important role in hemostasis, and NSAIDs affect platelet aggregation as well, use of TORADOL in patients who have coagulation disorders should be undertaken with caution, and those patients should be carefully monitored. Patients on therapeutic doses of anticoagulants (e.g., heparin or dicumarol derivatives) have an increased risk of bleeding complications if given TORADOL concurrently; physicians should administer such concomitant therapy with extreme caution. The concurrent use of TORADOL and prophylactic, low-dose heparin (2500-5000 units q12h) has not been studied extensively, but may also be associated with an increased risk of bleeding. Physicians should weigh the benefits against the risk, and exercise caution in using such concomitant therapy in these patients. In patients who receive anticoagulants for any reason, there is an increased risk of intramuscular hematoma formation from TORADOL IM injections (see PRECAUTIONS — Drug Interactions). In postmarketing experience, postoperative hematomas and other signs of wound bleeding have been reported in association with the perioperative use of TORADOL IM. Caution should be used, therefore, when TORADOL is administered pre- or intra-operatively. Perioperative use of TORADOL should be undertaken with caution when strict hemostasis is critical.

Information for Patients

TORADOL, like other drugs of its class, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS Sections) and likely benefits of TORADOL treatment, particularly when it is used for less serious conditions when lengthy treatment is anticipated and when acceptable alternatives to both the patient and physician may be available.

Laboratory Tests

Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow patients for the signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up (see PRECAUTIONS - Risk of GI Ulceration, Bleeding and Perforation).

Drug Interactions

TORADOL is highly bound to human plasma proteins (mean 99.2%) and binding is independent of concentration. The *in vitro* binding of ***warfarin*** to plasma proteins is only slightly reduced by TORADOL (99.5% control vs 99.3%) with TORADOL plasma concentrations of 5 to 10 µg/mL. TORADOL does not alter ***digoxin*** protein binding. *In vitro* studies indicate that, at therapeutic plasma concentrations of ***salicylate*** (300 µg/mL), the binding of TORADOL was reduced from approximately 99.2% to 97.5%, representing a potential two-fold increase in unbound TORADOL plasma levels; hence, TORADOL should be used with caution (or at a reduced dosage) in patients being treated with high-dose salicylate regimens. Therapeutic concentrations of ***digoxin, warfarin, ibuprofen, naproxen, piroxicam, acetaminophen, phenytoin,*** and ***tolbutamide*** did not alter TORADOL protein binding. In a study involving 12 volunteers, oral TORADOL was co-administered with a single dose of 25 mg ***warfarin***, causing no significant changes in pharmacokinetics or pharmacodynamics of warfarin. In another study, intramuscular TORADOL (following oral dosing) was given with two doses of 5000 U of ***heparin*** to 11 healthy volunteers, resulting in a mean template bleeding time of 6.4 minutes (3.2-11.4 min) compared to a mean of 6.0 minutes (3.4-7.5 min) for heparin alone and 5.1 minutes (3.5-8.5 min) for placebo. Although these results do not indicate a significant interaction between TORADOL and warfarin or heparin, the administration of TORADOL, or other NSAIDs, to patients taking anticoagulants should be done with caution and patients should be closely monitored (see PRECAUTIONS — Hematologic Effects). Intramuscular TORADOL reduced the diuretic response to ***furosemide*** in normovolemic healthy subjects by approximately 20% (mean sodium and urinary output decreased 17%). Concomitant administration of oral TORADOL and ***probenecid*** resulted in decreased clearance of ketorolac and significant increases in ketorolac plasma levels (total AUC increased approximately 3-fold from 5.4 to 17.8 µg•h/mL) and terminal half-life (increased approximately 2-fold from 6.6 to 15.1 hours). Inhibition of renal ***lithium*** clearance, leading to an increase in plasma lithium concentration, has been reported with some prostaglandin synthesis inhibiting drugs. The effect of TORADOL on plasma lithium has not been studied. Concomitant administration of ***methotrexate*** and some NSAIDs has been reported to reduce the clearance of methotrexate, enhancing the toxicity of methotrexate. The effect of TORADOL on methotrexate clearance has not been studied. In postmarketing experience, there have been three reports of a possible interaction between TORADOL IM and ***non-depolarizing muscle relaxants***, appearing to enhance the effect of the muscle relaxant. The concurrent use of TORADOL with muscle relaxants has not been formally studied. Intramuscular TORADOL has been administered concurrently with ***morphine*** in several clinical trials of postoperative pain without evidence of adverse interactions. There is no evidence, in animal or human studies, that TORADOL induces or inhibits hepatic enzymes capable of metabolizing itself or other drugs.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

An 18-month study in mice at oral doses of ketorolac tromethamine equal to the parenteral MRHD (Maximum Recommended Human Dose) and a 24-month study in rats at oral doses 2.5 times the parenteral MRHD, showed no evidence of tumorigenicity. Ketorolac tromethamine was not mutagenic in Ames test, unscheduled DNA synthesis and repair, and in forward mutation assays. Ketorolac did not cause chromosome breakage in the *in vivo* mouse micronucleus assay. At 1590 µg/mL (approximately 1000 times the average human plasma levels) and at higher concentrations, ketorolac tromethamine increased the incidence of chromosomal aberrations in Chinese hamster ovarian cells. Impairment of fertility did not occur in male or female rats at oral doses of 9 mg/kg (53.1 mg/m^2) and 16 mg/kg (94.4 mg/m^2), respectively.

Pregnancy

Pregnancy Category C

Reproduction studies have been performed in rabbits, using daily oral doses at 3.6 mg/kg (42.35 mg/m^2) and in rats at 10 mg/kg (59 mg/m^2) during organogenesis. Results of these studies did not reveal evidence of teratogenicity to the fetus. Oral doses of ketorolac tromethamine at 1.5 mg/kg (8.8 mg/m^2), which was half of the human oral exposure, administered after gestation day 17 caused dystocia and higher pup mortality in rats. There are no adequate and well-controlled studies in pregnant women. Ketorolac tromethamine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

TORADOL is not recommended for use during labor and delivery (see INDICATIONS and USAGE section of full prescribing information).

Lactation and Nursing

After a single administration of 10 mg of TORADOL ORAL to humans, the

TORADOL® IM and TORADOL® ORAL
(ketorolac tromethamine)

maximum milk concentration observed was 7.3 ng/mL and the maximum milk-to-plasma ratio was 0.037. After one day of dosing (qid), the maximum milk concentration was 7.9 ng/mL and the maximum milk-to-plasma ratio was 0.025. Caution should be exercised when TORADOL IM or ORAL is administered to a nursing woman.

Pediatric Use

Safety and efficacy in children have not been established. Therefore, TORADOL is not recommended for use in children.

Use in the Elderly

Because ketorolac tromethamine is cleared somewhat more slowly by the elderly (see CLINICAL PHARMACOLOGY section of full prescribing information) who are also more sensitive to the renal effects of NSAIDs (see PRECAUTIONS — Renal Effects), extra caution and reduced dosages (see DOSAGE AND ADMINISTRATION section of full prescribing information) should be used when treating the elderly with TORADOL.

ADVERSE REACTIONS

Adverse reaction rates from short-term use of NSAIDs are generally from 1/10 to 1/2 the rates associated with long-term use. This is also true for TORADOL. Adverse reaction rates also may increase with higher doses of TORADOL (see WARNINGS, and DOSAGE AND ADMINISTRATION section of full prescribing information). TORADOL IM is indicated for short-term use. Physicians using TORADOL IM should be alert for the usual complications of NSAID treatment, and should be aware that with longer use (exceeding 5 days) of TORADOL IM, the frequency and severity of adverse reactions may increase. Physicians using TORADOL ORAL should be alert to the relative risks associated with dose and dose duration as described in CLINICAL PHARMACOLOGY — Clinical Studies section of full prescribing information. Physicians using TORADOL should be alert for the usual complications of NSAID treatment. The adverse reactions listed below were reported in clinical trials with TORADOL in which patients received up to 20 doses, in 5 days, of TORADOL IM 30 mg or up to 4 doses a day from long-term studies of TORADOL ORAL 10 mg qid. In addition, adverse reactions that were reported from TORADOL IM postmarketing surveillance are included in "Incidence 1% or Less." **Incidence Greater than 1%** (probably causally related): **Body as a Whole:** EDEMA*; **Cardiovascular:** HYPERTENSION; **Dermatologic:** RASH, pruritus*; **Gastrointestinal:** NAUSEA (12%), DYSPEPSIA (12%), GASTROINTESTINAL PAIN (13%), constipation, diarrhea*, flatulence, gastrointestinal fullness, vomiting, STOMATITIS; **Hemic and Lymphatic:** purpura; **Nervous System:** drowsiness*, dizziness*, HEADACHE (17%), sweating. Injection site pain was reported by 2% of patients in multidose studies (vs. 5% for the morphine control group). *Incidence of reported reaction between 3% and 9%. Those reactions occurring in less than 3% of the patients are unmarked. Reactions reported predominantly from long-term TORADOL ORAL studies are CAPITALIZED. **Incidence 1% or Less** (probably causally related): **Body as a Whole:** hypersensitivity reactions such as *anaphylaxis*[1], *bronchospasm, laryngeal edema, tongue edema, hypotension*, and *flushing*, weight gain, fever; **Cardiovascular:** flushing, palpitation, pallor, *hypotension*, syncope; **Dermatologic:** *Lyell's syndrome, Stevens-Johnson syndrome, exfoliative dermatitis, maculo-papular rash*, urticaria; **Gastrointestinal:** *peptic ulceration, GI hemorrhage, GI perforation* (see WARNINGS and PRECAUTIONS), *melena*, rectal bleeding, gastritis, eructation, anorexia, increased appetite; **Hemic and Lymphatic:** *postoperative wound hemorrhage*, rarely requiring blood transfusion (see WARNINGS and PRECAUTIONS), *thrombocytopenia*, epistaxis, anemia; **Nervous System:** *convulsions*, vertigo, tremors, abnormal dreams, hallucinations, euphoria; **Respiratory:** dyspnea, *asthma*, pulmonary edema; **Urogenital:** *acute renal failure* (see WARNINGS and PRECAUTIONS), *flank pain with or without hematuria and/or azotemia*, oliguria, nephritis.

[1] *Italics* denote reactions reported from *postmarketing experience*.

Other Adverse Events (causal relationship unknown)[2]: **Body as a Whole:** asthenia; **Gastrointestinal:** *pancreatitis*; **Hemic and Lymphatic:** *leukopenia*, EOSINOPHILIA; **Nervous System:** paresthesia, depression, insomnia, nervousness, excessive thirst, dry mouth, abnormal thinking, inability to concentrate, hyperkinesia, stupor; **Respiratory:** RHINITIS, COUGH, dyspnea; **Special Senses:** abnormal taste, abnormal vision, blurred vision, tinnitus, HEARING LOSS; **Urogenital:** polyuria, increased urinary frequency.

[2] Reactions occurred under circumstances where the causal relationship to TORADOL treatment has not been clearly established; they are presented as alerting information for physicians. Reactions reported predominantly from long-term TORADOL ORAL studies are CAPITALIZED.

See package insert for full prescribing information.

CAUTION: Federal law prohibits dispensing without prescription.

U.S. Patent No. 4,089,969 and others

SYNTEX

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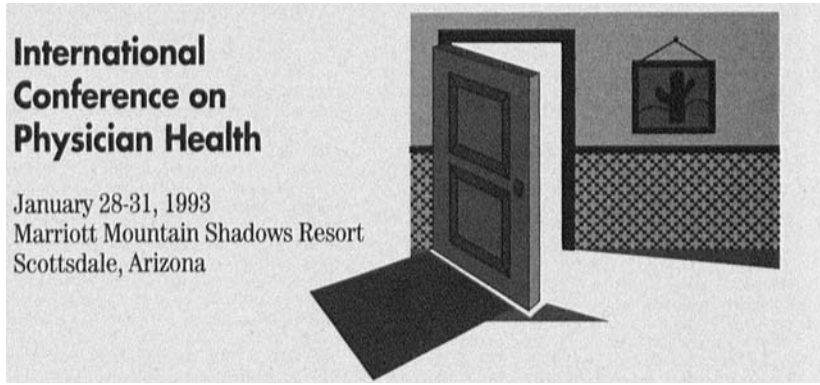
April 1992
02-2435-00-01
PO92152

Opening Doors to Physician Health



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- Mental illness in physicians
- Physicians with physical limitations
- HIV infection among physicians

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There is only one automatic Epinephrine Injection.

For self administration in any allergic emergency...

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Just remove safety cap and press into thigh.

Brief summary: Before prescribing, please consult package insert.

DESCRIPTION: The EpiPen Auto-Injectors contain 2 mL Epinephrine Injection for emergency intramuscular use. Each EpiPen Auto-Injector delivers a single dose of 0.3 mg epinephrine from Epinephrine Injection, USP, 1:1000 (0.3 mL) in a sterile solution. Each EpiPen Jr. Auto Injector delivers a single dose of 0.15 mg epinephrine from Epinephrine Injection, USP, 1:2000 (0.3 mL) in a sterile solution. Each 0.3 mL also contains 1.8 mg sodium chloride, 0.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, and Water for Injection. The pH range is 2.5-5.0.

CLINICAL PHARMACOLOGY: Epinephrine is a sympathomimetic drug, acting on both alpha and beta receptors. It is the drug of choice for the emergency treatment of severe allergic reactions (Type 1) to insect stings or bites, foods, drugs, and other allergens. It can also be used in the treatment of idiopathic or exercise-induced anaphylaxis. Epinephrine when given subcutaneously or intramuscularly has a rapid onset and short duration of action.

INDICATIONS AND USAGE: Epinephrine is indicated in the emergency treatment of allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs and other allergens as well as idiopathic or exercise-induced anaphylaxis. The EpiPen Auto-Injector is intended for immediate self-administration by a person with a history of an anaphylactic reaction. Such reactions may occur within minutes after exposure and consist of flushing, apprehension, syncope, tachycardia, thready or unobtainable pulse associated with a fall in blood pressure, convulsions, vomiting, diarrhea and abdominal cramps, involuntary voiding, wheezing, dyspnea due to laryngeal spasm, pruritis, rashes, urticaria or angioedema. The EpiPen is designed as emergency supportive therapy only and is not a replacement or substitute for immediate medical or hospital care.

CONTRAINDICATIONS: There are no absolute contraindications to the use of epinephrine in a life-threatening situation.

WARNINGS: Epinephrine is light sensitive and should be stored in the tube provided. Store at room temperature (15°-30°C/59°-86°F). Do not refrigerate. Before using, check to make sure solution in Auto-Injector is not discolored. Replace the Auto-Injector if the solution is discolored or contains a precipitate. Avoid possible inadvertent intravascular administration. Select an appropriate injection site such as the thigh. DO NOT INJECT INTO BUTTOCK. Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure. DO NOT INJECT INTRAVENOUSLY. Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine.

Epinephrine is the preferred treatment for serious allergic or other emergency situations even though this product contains sodium metabisulfite, a sulfite that may in other products cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons. The alternatives to using epinephrine in a life-threatening situation may not be satisfactory. The presence of a sulfite in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations.

Accidental injection into the hands or feet may result in loss of blood flow to the affected area and should be avoided. If there is an accidental injection into these areas, go immediately to the nearest emergency room for treatment. EpiPen should ONLY be injected into the anteriolateral aspect of the thigh.

PRECAUTIONS: Epinephrine is ordinarily administered with extreme caution to patients who have heart disease. Use of epinephrine with drugs that may sensitize the heart to arrhythmias, e.g., digitalis, mercurial diuretics, or quinidine, ordinarily is not recommended. Anginal pain may be induced by epinephrine in patients with coronary insufficiency. The effects of epinephrine may be potentiated by tricyclic antidepressants and monoamine oxidase inhibitors. Hyperthyroid individuals, individuals with cardiovascular disease, hypertension, or diabetes, elderly individuals, pregnant women, and children under 30 kg (66 lbs.) body weight may be theoretically at greater risk of developing adverse reactions after epinephrine administration. Despite these concerns, epinephrine is essential for the treatment of anaphylaxis. Therefore, patients with these conditions, and/or any other person who might be in a position to administer EpiPen or EpiPen Jr. to a patient experiencing anaphylaxis should be carefully instructed in regard to the circumstances under which this life-saving medication should be used.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Studies of epinephrine in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

USAGE IN PREGNANCY: Pregnancy Category C: Epinephrine has been shown to be teratogenic in rats when given in doses about 25 times the human dose. There are no adequate and well-controlled studies in pregnant women. Epinephrine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

PEDIATRIC USE: Epinephrine may be given safely to children at a dosage appropriate to body weight (see Dosage and Administration).

ADVERSE REACTIONS: Side effects of epinephrine may include palpitations, tachycardia, sweating, nausea and vomiting, respiratory difficulty, pallor, dizziness, weakness, tremor, headache, apprehension, nervousness and anxiety. Cardiac arrythmias may follow administration of epinephrine.

OVERDOSAGE: Overdosage or inadvertent intravascular injection of epinephrine may cause cerebral hemorrhage resulting from a sharp rise in blood pressure. Fatalities may also result from pulmonary edema because of peripheral vascular constriction together with cardiac stimulation.

DOSAGE AND ADMINISTRATION: Usual epinephrine adult dose for allergic emergencies is 0.3 mg. For pediatric use, the appropriate dosage may be 0.15 or 0.30 mg depending upon the body weight of the patient. However, the prescribing physician has the option of prescribing more or less than these amounts, based on careful assessment of each individual patient and recognizing the life-threatening nature of the reactions for which this drug is being prescribed. With severe persistant anaphylaxis, repeat injections with an additional EpiPen may be necessary.

HOW SUPPLIED: EpiPen and EpiPen Jr. Auto-Injectors are available singly or in packages of twelve.

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

Issued: April 1992

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Because coexisting conditions often complicate hypertension...

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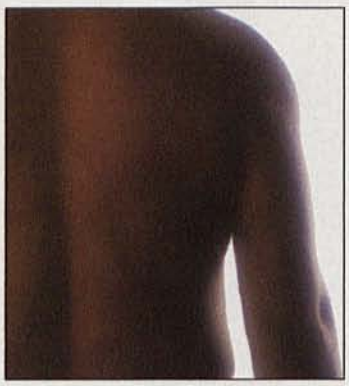
(isradipine)

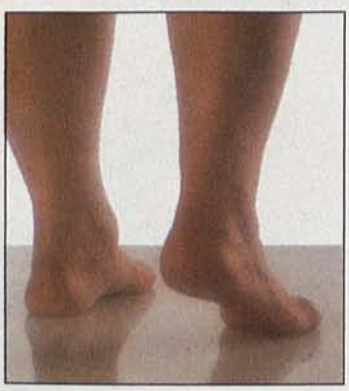


Facilitates renal function.

- No clinically significant change in serum creatinine[1,2] or creatinine clearance[1,3]
- No clinically significant effect on glomerular filtration rate[3-6]
- Maintains or decreases filtration fraction[1,3,6]

Maintains cardiac performance.

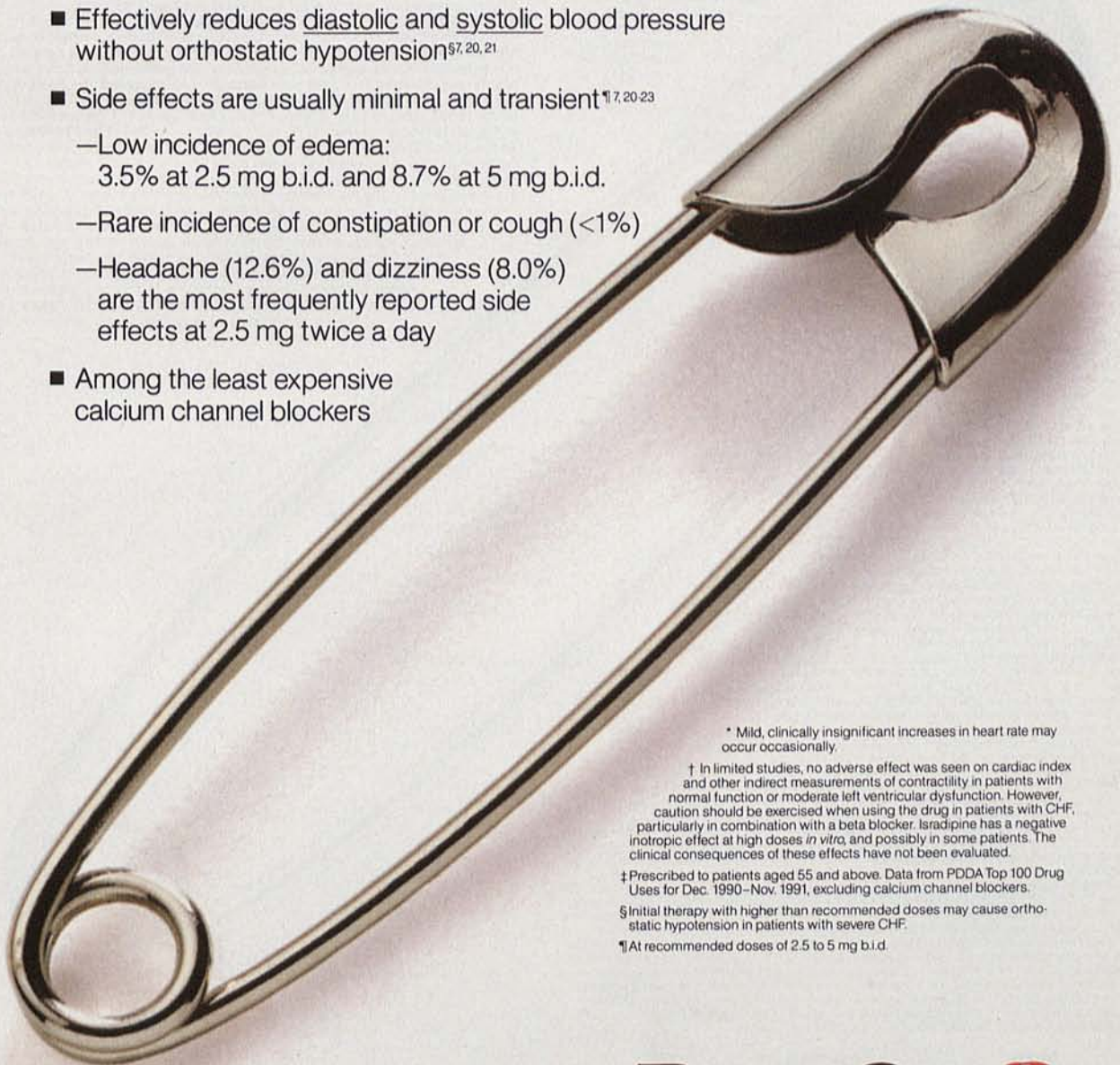
- No significant effect on heart rate*[7-10]
- No adverse effect on cardiac conduction[11,12] or contractility†[3,10,13-15]
- No alteration of digoxin clearance[16]



Does not compromise metabolic parameters.

- No clinically significant effect on serum glucose metabolism[17]
- No effect on glucose tolerance, insulin secretion or insulin action in NIDDM patients[17]
- No clinically significant effect on lipid metabolism[18,19]

- No known contraindications except for hypersensitivity to DynaCirc
- No significant interactions with the 20 most-commonly prescribed drugs‡
- Effectively reduces diastolic and systolic blood pressure without orthostatic hypotension§[7, 20, 21]
- Side effects are usually minimal and transient¶[7, 20-23]
  - —Low incidence of edema: 3.5% at 2.5 mg b.i.d. and 8.7% at 5 mg b.i.d.
  - —Rare incidence of constipation or cough (<1%)
  - —Headache (12.6%) and dizziness (8.0%) are the most frequently reported side effects at 2.5 mg twice a day
- Among the least expensive calcium channel blockers



* Mild, clinically insignificant increases in heart rate may occur occasionally.

† In limited studies, no adverse effect was seen on cardiac index and other indirect measurements of contractility in patients with normal function or moderate left ventricular dysfunction. However, caution should be exercised when using the drug in patients with CHF, particularly in combination with a beta blocker. Isradipine has a negative inotropic effect at high doses *in vitro*, and possibly in some patients. The clinical consequences of these effects have not been evaluated.

‡ Prescribed to patients aged 55 and above. Data from PDDA Top 100 Drug Uses for Dec. 1990–Nov. 1991, excluding calcium channel blockers.

§ Initial therapy with higher than recommended doses may cause orthostatic hypotension in patients with severe CHF.

¶ At recommended doses of 2.5 to 5 mg b.i.d.

DynaCirc®

2.5 mg capsules (isradipine) 5 mg capsules

For Safety's Sake™

Please see following page for brief summary of full Prescribing Information.

BRIEF SUMMARY
Please see package insert for full prescribing information.

DYNACIRC® (isradipine) CAPSULES

INDICATION

DynaCirc® (isradipine) is indicated in the management of hypertension. It may be used alone or concurrently with thiazide-type diuretics.

CONTRAINDICATIONS

DynaCirc® is contraindicated in individuals who have shown hypersensitivity to any of the ingredients in the formulation.

WARNINGS

None.

PRECAUTIONS

General: *Blood Pressure:* Because DynaCirc® decreases peripheral resistance, like other calcium blockers DynaCirc® may occasionally produce symptomatic hypotension. However, symptoms like syncope and severe dizziness have rarely been reported in hypertensive patients administered DynaCirc®, particularly at the initial recommended doses. *Use in Patients with Congestive Heart Failure:* Although acute hemodynamic studies in patients with congestive heart failure have shown that DynaCirc® reduced afterload without impairing myocardial contractility, it has a negative inotropic effect at high doses *in vitro*, and possibly in some patients. Caution should be exercised when using the drug in congestive heart failure patients, particularly in combination with a beta-blocker. **Drug Interactions:** *Nitroglycerin:* DynaCirc® has been safely coadministered with nitroglycerin. *Hydrochlorothiazide:* A study in normal healthy volunteers has shown that concomitant administration of DynaCirc® and hydrochlorothiazide does not result in altered pharmacokinetics of either drug. In a study in hypertensive patients, addition of isradipine to existing hydrochlorothiazide therapy did not result in any unexpected adverse effects, and isradipine had an additional antihypertensive effect.

Propranolol: In a single dose study in normal volunteers coadministration of propranolol had a small effect on the rate but no effect on the extent of isradipine bioavailability. Coadministration of DynaCirc® resulted in significant increases in AUC (27%) and C_{max} (58%) and decreases in t_{max} (23%) of propranolol. *Digoxin:* The concomitant administration of DynaCirc® and digoxin in a single-dose pharmacokinetic study did not affect renal, nonrenal and total body clearance of digoxin. *Fentanyl Anesthesia:* Severe hypotension has been reported during fentanyl anesthesia with concomitant use of a beta blocker and a calcium channel blocker. Even though such interactions have not been seen in clinical studies with DynaCirc®, an increased volume of circulating fluids might be required if such an interaction were to occur. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Treatment of male rats for 2 years with 2.5, 12.5, or 62.5 mg/kg/day isradipine admixed with the diet resulted in dose dependent increases in the incidence of benign Leydig cell tumors and testicular hyperplasia relative to untreated control animals. A comparable endocrine effect was not evident in male patients receiving therapeutic doses of the drug on a chronic basis. Treatment of mice for two years with 2.5, 15, or 80 mg/kg/day isradipine in the diet showed no evidence of oncogenicity. There was no evidence of mutagenic potential based on the results of a battery of mutagenicity tests. No effect on fertility was observed in male and female rats. **Pregnancy:** *Pregnancy Category C:* There are no adequate and well controlled studies in pregnant women. DynaCirc® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers:** It is not known whether DynaCirc® is excreted in human milk. A decision should be made as to whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** Safety and effectiveness have not been established in children.

ADVERSE REACTIONS

The adverse reaction rates given below are principally based on controlled hypertension studies, but rarer serious events are derived from all exposures to DynaCirc®, including foreign marketing experience. Most adverse reactions were mild and related to the vasodilatory effects of DynaCirc® (dizziness, edema, palpitations, flushing, tachycardia), and many were transient. About 5% of isradipine patients left studies prematurely because of adverse reactions (vs. 3% of placebo patients and 6% of active control patients), principally due to headache, edema, dizziness, palpitations, and gastrointestinal disturbances. The following adverse reactions have been reported by 1% or greater of patients receiving DynaCirc® at any dose (N=934): headache (13.7%), dizziness (7.3%), edema (7.2%), palpitations (4.0%), fatigue (3.9%), flushing (2.6%), chest pain (2.4%), nausea (1.8%), dyspnea (1.8%), abdominal discomfort (1.7%), tachycardia (1.5%), rash (1.5%), pollakiuria (1.5%), weakness (1.2%), vomiting (1.1%), diarrhea (1.1%). The following adverse events were reported in 0.5-1% of the isradipine-treated patients in hypertension studies, or are rare, but more serious events from this and other data sources, including postmarketing exposure, are shown in italics. The relationship of these adverse events to isradipine administration is uncertain. **Skin:** pruritus, *urticaria.* **Musculoskeletal:** cramps of legs/feet. **Respiratory:** cough. **Cardiovascular:** shortness of breath, hypotension, *atrial fibrillation, ventricular fibrillation, myocardial infarction, heart failure.* **Gastrointestinal:** abdominal discomfort, constipation, diarrhea. **Urogenital:** nocturia. **Nervous System:** drowsiness, insomnia, lethargy, nervousness, impotence, decreased libido, depression, *syncope, paresthesia* (which includes numbness and tingling), *transient ischemic attack, stroke.* **Autonomic:** hyperhidrosis, visual disturbance, dry mouth, numbness. **Miscellaneous:** throat discomfort, *leukopenia, elevated liver function tests.*

[DECEMBER 31, 1990 DYN-Z2]

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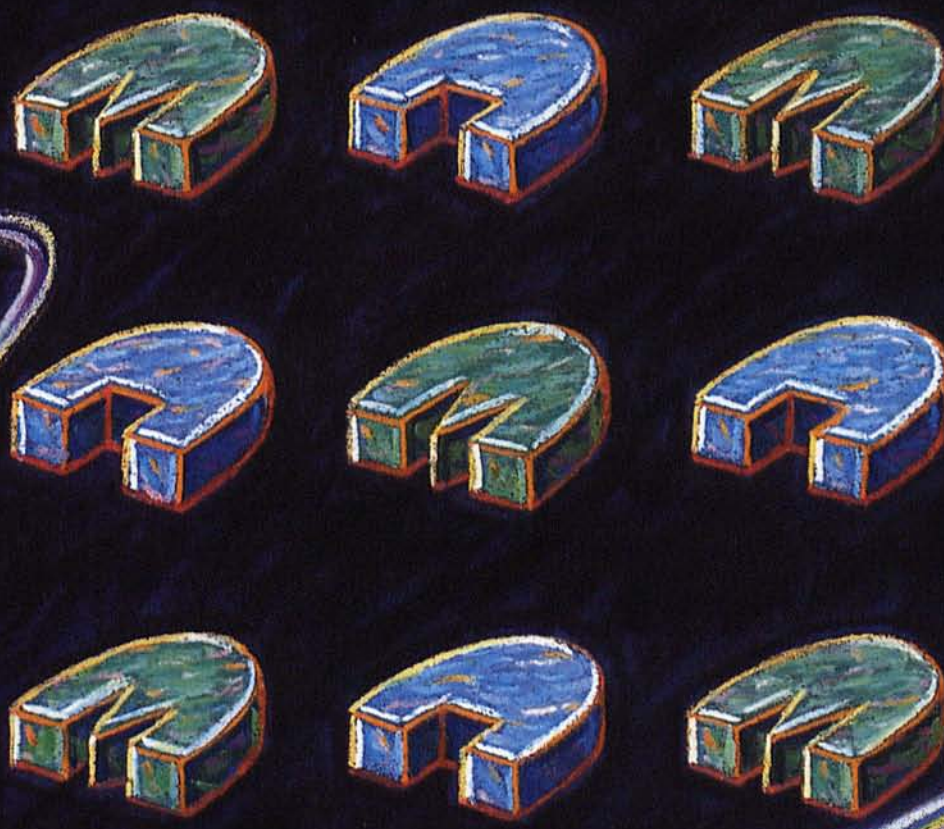

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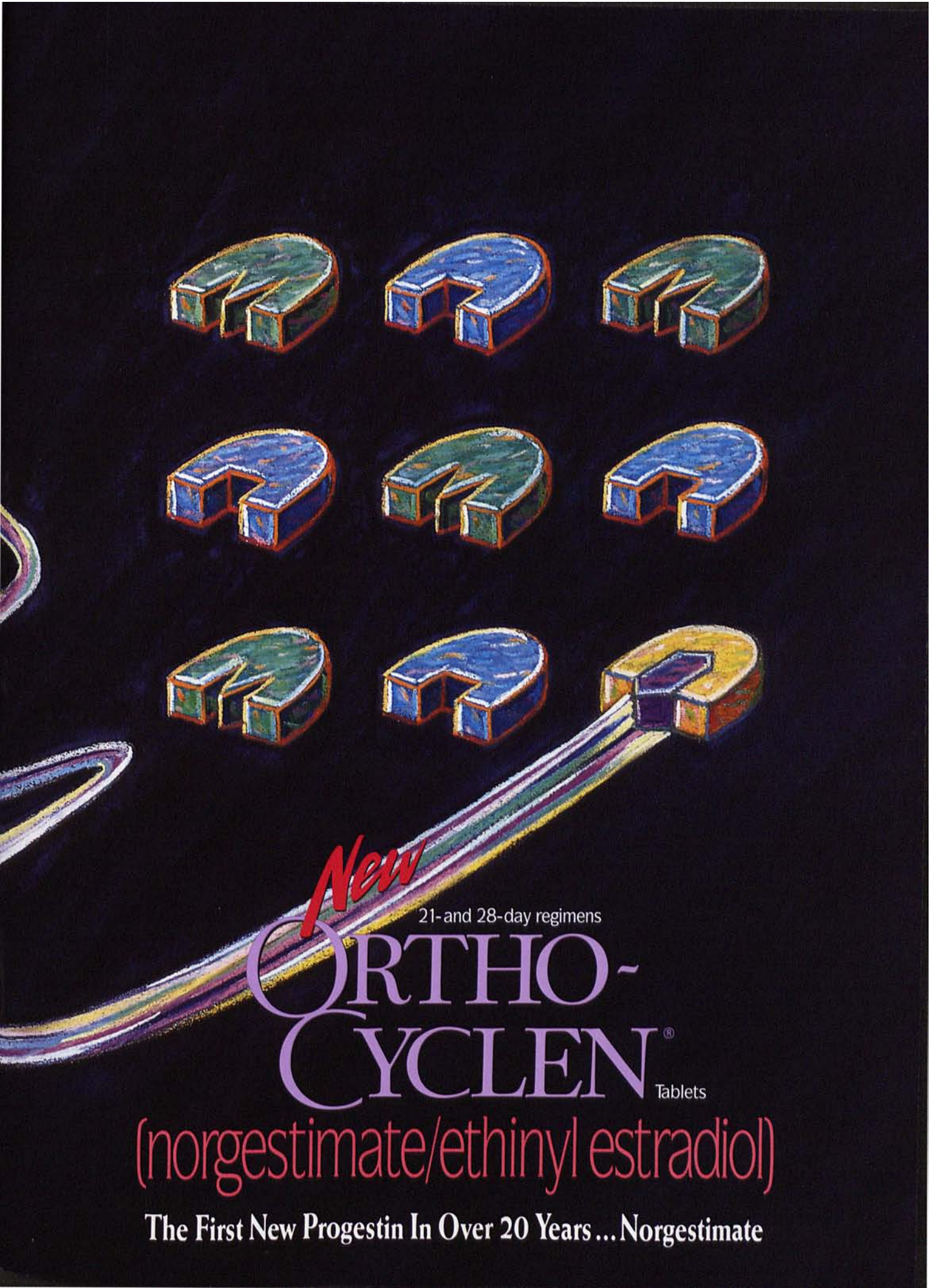
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INDICATIONS: Acute and long-term treatment of signs and symptoms of rheumatoid arthritis and osteoarthritis.

CONTRAINDICATIONS: ANSAID is contraindicated in patients who have previously demonstrated hypersensitivity to it. ANSAID should not be given to patients in whom ANSAID, aspirin, or other nonsteroidal anti-inflammatory drugs induce asthma, urticaria, or other allergic-type reactions. Fatal asthmatic reactions have been reported in such patients receiving this type of drug.

WARNINGS: Risk of Gastrointestinal (GI) Ulcerations, Bleeding, and Perforation With Nonsteroidal Anti-inflammatory Therapy: Serious GI toxicity can occur at any time, with or without warning symptoms, during chronic treatment. Minor upper GI problems, such as dyspepsia, are common and usually develop early in therapy; however, remain alert for ulceration and bleeding during chronic treatment, even in the absence of previous GI tract problems. In clinical trials, symptomatic upper GI ulcers, gross bleeding, or perforation occurred in about 1% of patients treated for 3 to 6 months and in about 2% to 4% treated for 1 year. Inform patients of signs and symptoms of serious GI toxicity and what to do if they occur. No subset of patients not at risk has been identified. Except for a prior history of serious GI events and other risk factors associated with peptic ulcer disease (eg, alcoholism, smoking, etc), no risk factors have been associated with increased risk (eg, age, sex). The elderly and debilitated tolerate ulceration and bleeding less well, and most spontaneous reports of fatal GI events are in this population. Study data are inconclusive concerning the relative risk of various nonsteroidal anti-inflammatory agents in causing such reactions. High doses probably carry a greater risk, although controlled clinical trials showing this do not exist in most cases. When considering use of relatively large doses (within recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity. GI ulceration and bleeding can occur without warning symptoms, and patients treated chronically should be followed and informed of the importance of this follow-up.

PRECAUTIONS: General: Impaired Renal or Hepatic Function: Use ANSAID cautiously. Pharmacokinetics have not been studied in patients with decreased liver function. **Renal Effects:** Rats developed renal papillary necrosis at dosages equivalent to human therapeutic levels, as did monkeys given 20 to 40 times the human dose. In clinical studies of ANSAID, renal effects were similar to those seen with other nonsteroidal anti-inflammatory drugs. A second form of renal toxicity has been seen in patients with prerenal conditions that reduce renal blood flow or blood volume. A nonsteroidal anti-inflammatory drug may cause dose-dependent reduction in prostaglandin formation and precipitate overt renal decompensation. Patients with impaired renal or hepatic function, heart failure, those taking diuretics, and the elderly are at greatest risk. Drug discontinuation usually leads to recovery. Monitor renal function in high-risk patients on chronic treatment if they have signs or symptoms that may be consistent with mild azotemia, eg, malaise, fatigue, loss of appetite, etc. Occasionally BUN and serum creatinine may be elevated without signs or symptoms. Flurbiprofen metabolites primarily are excreted by the kidneys, and elimination of 4′-hydroxy-flurbiprofen is markedly reduced by end-stage renal disease. Therefore, monitor patients with significantly impaired renal function, and consider reducing dosage to avoid accumulation of flurbiprofen metabolites. **Liver Tests:** Borderline elevations of liver function tests may occur in up to 15% of patients and may progress, remain unchanged, or disappear with continued treatment. Meaningful elevations of ALT or AST (SGOT) were reported in less than 1% of patients in controlled clinical trials. Patients with signs or symptoms, or both, suggesting liver dysfunction or with an abnormal liver function test require further evaluation. **Anemia:** Anemia may be aggravated. Determine hemoglobin values periodically in patients treated long-term who have initial hemoglobin values under 10 g/dL. **Fluid Retention and Edema:** Fluid retention and edema have been reported; use ANSAID with caution in patients with conditions such as cardiac decompensation or hypertension. **Vision Changes:** Blurred or diminished vision, or both, has been reported. Patients with eye complaints should have ophthalmologic exams. **Effect on Platelets and Coagulation:** Platelet aggregation is inhibited, and bleeding time has been prolonged after single and multiple oral doses. Carefully observe patients who may be adversely affected. **Information for Patients:** Because the side effects of ANSAID, like those of other drugs in its class, can cause discomfort and, rarely, hospitalization, and even fatal outcomes, physicians and patients may wish to discuss potential risks (see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections) and likely benefits. **Drug Interactions: Antacids:** In young volunteers, the administration of ANSAID under fasting conditions or with antacid suspension yielded similar serum flurbiprofen-time profiles. Rate, but not the extent of flurbiprofen absorption, was reduced in geriatric volunteers. **Anticoagulants:** Bleeding parameters are affected, and serious bleeding has been reported; use with caution. **Aspirin:** Flurbiprofen levels were 50% lower with concomitant administration; concurrent use is not recommended. **ß-Adrenergic blocking agents:** Flurbiprofen pretreatment attenuated the hypotensive effect of a single dose of propranolol but not atenolol in men with mild uncomplicated hypertension; pharmacokinetics and heart-rate reduction were not affected. Monitor patients taking both flurbiprofen and a ß-blocker to ensure that a satisfactory hypotensive effect is achieved. **Cimetidine, ranitidine:** In volunteers, cimetidine caused a 13% increase in area under the flurbiprofen serum concentration curve. **Digoxin:** Studies in healthy men did not show a change in steady-state serum levels of either drug. **Diuretics:** Studies in normal volunteers show that flurbiprofen can interfere with the effects of furosemide. Nonsteroidal anti-inflammatory drugs that inhibit prostaglandin synthesis have been shown to interfere with thiazide diuretics in some studies and with potassium-sparing diuretics. Closely observe patients receiving furosemide or other diuretics to make sure the desired effects are obtained. **Oral hypoglycemic agents:** In one study, there was a slight reduction in blood sugar concentrations during concomitant administration of flurbiprofen and glyburide, metformin, chlorpropamide with phenformin, or glyburide with phenformin; however, there were no signs or symptoms of hypoglycemia. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** No evidence of carcinogenesis or fertility impairment. **Teratogenic Effects: Pregnancy Category B:** No teratogenic effects in animals. Not recommended for use in pregnancy. **Labor and Delivery, Nursing Mothers, Pediatric Use:** Use is not recommended during late pregnancy or in nursing mothers. Safety and efficacy have not been established in children.

ADVERSE REACTIONS: In premarketing studies, 9.4% of 4,123 patients dropped out because of adverse events. **Incidence > 1%:** (* = occurred in 3% to 9% of patients) Gastrointestinal - Dyspepsia,* diarrhea,* abdominal pain,* nausea,* constipation, GI bleeding, flatulence, elevated liver enzymes, and vomiting. Central nervous system - Headache,* CNS "stimulation" (eg, nervousness, anxiety, insomnia, reflexes increased, and tremor), and CNS "inhibition" (eg, amnesia, asthenia, somnolence, malaise, and depression). Respiratory - Rhinitis. Dermatologic - Rash. Special senses - Dizziness, tinnitus, and vision changes. Genitourinary - Signs and symptoms suggesting a urinary tract infection.* Body as a whole - Edema.* Metabolic/Nutritional - Body weight changes. **Incidence < 1% (Causal Relationship Probable):** Gastrointestinal - Peptic ulcer disease (see WARNINGS), gastritis, bloody diarrhea, stomatitis, esophageal disease, hematemesis, hepatitis, and cholestatic and noncholestatic jaundice. Central nervous system - ataxia, cerebrovascular ischemia, confusion, paresthesia, and twitching. Hematologic - Decrease in hemoglobin and hematocrit, iron deficiency anemia, hemolytic anemia, aplastic anemia, leukopenia, eosinophilia, ecchymosis, and thrombocytopenia (see PRECAUTIONS). Respiratory - Asthma and epistaxis. Dermatologic - Angioedema, urticaria, eczema, pruritus, photosensitivity, toxic epidermal necrolysis, and exfoliative dermatitis. Special senses - Conjunctivitis and parosmia. Genitourinary - Hematuria, renal failure, and interstitial nephritis. Body as a whole - chills, fever, and anaphylactic reaction. Metabolic/Nutritional - Hyperuricemia. Cardiovascular - Heart failure, hypertension, vascular diseases, and vasodilation. **Incidence < 1% (Causal Relationship Unknown):** Gastrointestinal - Periodontal abscess, appetite changes, cholecystitis, and dry mouth. Central nervous system - Convulsion, meningitis, hypertonia, cerebrovascular accident, emotional lability, and subarachnoid hemorrhage. Hematologic - Lymphadenopathy. Respiratory - Bronchitis, laryngitis, dyspnea, pulmonary embolism, pulmonary infarct, and hyperventilation. Dermatologic - Alopecia, nail disorder, herpes simplex and zoster, dry skin, and sweating. Special senses - Ear disease, corneal opacity, glaucoma, retrobulbar neuritis, taste change, transient hearing loss, and retinal hemorrhage. Genitourinary - Menstrual disturbances, vaginal and uterine hemorrhage, vulvovaginitis, and prostate disease. Metabolic/Nutritional - Hyperkalemia. Cardiovascular - Arrhythmias, angina pectoris, and myocardial infarction. Musculoskeletal - Myasthenia.

OVERDOSAGE: Although some overdoses in children have produced no symptoms (200 mg to 2.5 g ingested), the following have occurred in children who ingested 150 to 800 mg: drowsiness, dilated pupils, semiconsciousness, pinpoint pupils, diminished tone, and elevated enzymes. Although some overdoses in adults have produced no symptoms (3 g to 5 g ingested), the following have occurred in adults who ingested 1 g to 6 g: coma and respiratory depression, drowsiness, nausea, epigastric pain, dizziness, headache, and agitation. One 70-year-old man with a history of chronic obstructive airway disease died; toxicologic analysis showed acute flurbiprofen overdose and a blood alcohol concentration of 100 mg/dL. One patient who took 200 mg to 400 mg of flurbiprofen and 2.4 g of fenoprofen had disorientation and diplopia. Treat overdose with vomiting or lavage and supportive treatment; some patients have been given supplemental oral or intravenous fluids and required no further treatment.

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

Caution: Federal law prohibits dispensing without a prescription.

B-2-S

Upjohn The Upjohn Company
Kalamazoo, MI 49001, USA

USJ 8089.00

November 1992

FOR PEOPLE WITH ARTHRITIS

THE OBSTACLE COURSE...

THE RECOURSE

Helping overcome life's obstacles

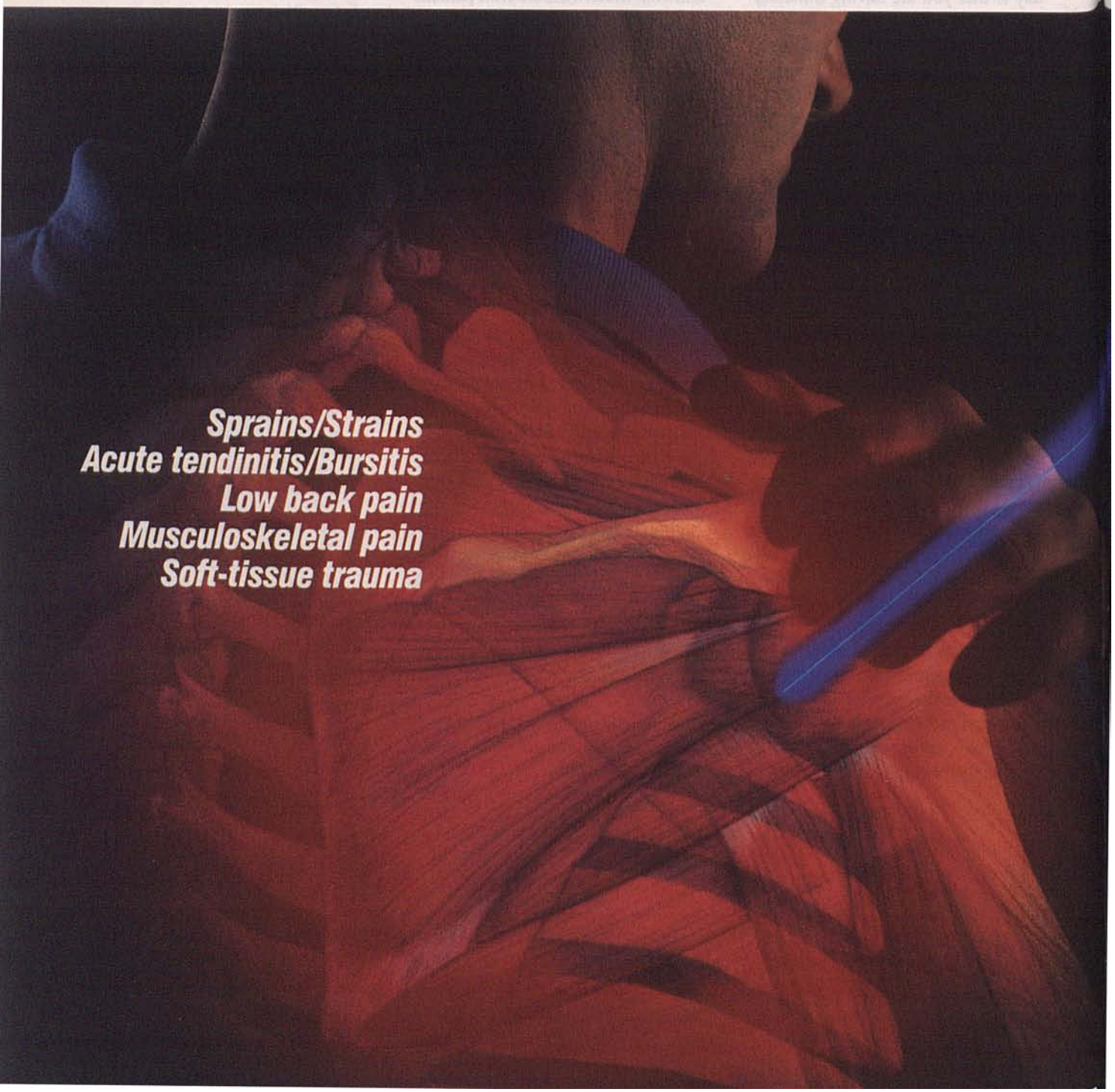
Ansaid® 100 mg Tablets

FLURBIPROFEN

*The average prescribed daily dose is 100 mg bid. Data on file with The Upjohn Company.
As with other nonsteroidal agents, the most frequent side effect is mild gastrointestinal disturbances.

For a brief summary of prescribing information, please turn the page.

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.

 811-J2-505-92

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 even in the absence of previous GI tract symptoms. In clinical trials, symptomatic upper GI ulcers, gross bleeding or perforation occur in about 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Inform patients of 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 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 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®** OR **ANAPROX® DS** (NAPROXEN SODIUM) SINCE THEY 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 dosa in the elderly or in patients with chronic alcoholic liver disease or cirrhosis. Borderline elevations of liver tests may occur in up to 15% of patients. Elevations of SGPT or SGOT occurred in controlled 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. For patients with restricted sodium intake, note that each tablet contains approximately 25 or 50 mg (1 or 2 mEq) sodium. Use with caution in patients with fluid retention, hypertension or heart failure. The drug may reduce fever and inflammation, diminishing their diagnostic value. Conduct ophthalmic studies if any change or disturbance in vision occurs. **Information for Patients:** Side effects can cause discomfort and, rarely, more serious side effects, such as GI bleeding, may result in hospitalization and even fatal outcomes. Physicians may wish to discuss with patients potential risks and benefits of NSAIDs, particularly when they are used for less serious conditions where treatment without NSAIDs may be acceptable. 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 and inform them of the importance of the 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:** May decrease platelet aggregation and prolong bleeding time or increase urinary values for 17-ketogenic steroids. Temporarily stop therapy for 72 hours before adrenal function tests. 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. **Pediatric Use:** Single doses of 2.5-5 mg/kg (as naproxen suspension), 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 1650 mg/day naproxen sodium than in those on 825 mg/day. 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 of reported reaction 3%-9%. Where unmarked, incidence less than 3%. 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.
Dosage and Administration for Mild to Moderate Pain, Dysmenorrhea and Acute Tendinitis and Bursitis: Recommended starting dose is 550 mg, followed by 275 mg every 6 to 8 hours. Total daily dose should not exceed 1375 mg.
Dosage and Administration for Rheumatoid Arthritis, Osteoarthritis and Ankylosing Spondylitis: Recommended dose in adults is 275 mg or 550 mg twice daily. In patients who tolerate lower doses well, the dose may be increased to 1650 mg per day for limited periods when a higher level of anti-inflammatory/analgesic activity is required. At this dosage, physicians should observe sufficient increased clinical benefits to offset potential increased risk.
Caution: Federal law prohibits dispensing without prescription.
See package insert for full Prescribing Information.

#35 Revised 9/91

SYNTEX
SYNTEX PUERTO RICO INC.
HUMACAO PR 00661

550 MG TABLETS **Anaprox DS** 275 MG TABLETS **Anaprox**
(NAPROXEN SODIUM)

Specify "Dispense As Written"

A Shape Of Quality

Potassium and magnesium conservation[1,2] with the optimal ratio (1.5 to1) of triamterene to hydrochlorothiazide[3]

79% of mildly hypertensive patients normalized* within 4 weeks[1†]

Twice the bioavailability of Dyazide®[3‡]

The Shape to Remember

Once-a-day **MAXZIDE®-25 MG**

Triamterene **37.5 mg**/Hydrochlorothiazide **25 mg**

* Diastolic BP < 90 mmHg.

† MAXZIDE-25 MG is indicated for the treatment of hypertension or edema in patients who develop hypokalemia on hydrochlorothiazide alone or in whom the development of hypokalemia cannot be risked.

‡ Dyazide is a registered trademark of SmithKline Beecham Pharmaceuticals.

® Unique tablet shape is a registered trademark of American Cyanamid Company.

Please see adjacent page for brief summary of full Prescribing Information.

Specify

"Dispense As Written"

Effectively controls mild-to-moderate hypertension and potassium loss[1]

The Shape to Remember

Once-a-day MAXZIDE®-25 MG

Triamterene 37.5 mg/Hydrochlorothiazide 25 mg

MAXZIDE® and MAXZIDE®-25 MG Tablets
Triamterene and Hydrochlorothiazide

Brief Summary
Please see package insert for full prescribing information.

INDICATIONS AND USAGE
This fixed combination drug is not indicated for the initial therapy of edema or hypertension except in individuals in whom the development of hypokalemia cannot be risked.

CONTRAINDICATIONS
Elevated serum potassium levels (≥5.5 mEq/L). Discontinue if hyperkalemia develops. Concomitant use with other potassium-sparing agents. Concomitant potassium supplementation. Anuria, acute and chronic renal insufficiency, significant renal impairment. Hypersensitivity to either component or to other sulfonamide-derived drugs.

WARNINGS
Hyperkalemia: Abnormal elevation of serum potassium levels (≥5.5 mEq/L) can occur with all potassium-conserving agents including MAXZIDE. Hyperkalemia is more likely to occur in patients with renal impairment, diabetes (even without evidence of renal impairment), or elderly or severely ill patients. Since uncorrected hyperkalemia may be fatal, serum potassium levels must be monitored at frequent intervals, especially in patients first receiving MAXZIDE, when dosages are changed, or with any illness that may influence renal function.

Obtain ECG if signs and symptoms of hyperkalemia occur. Discontinue MAXZIDE immediately if hyperkalemia is present. If the serum potassium level exceeds 6.5 mEq/L, more vigorous therapy is required. Avoid MAXZIDE in diabetic patients. If used, monitor serum electrolytes. Avoid in severely ill patients in whom respiratory or metabolic acidosis may occur. If MAXZIDE is used, frequently evaluate acid/base and serum electrolytes.

Use cautiously, if at all, with angiotensin-converting enzyme (ACE) inhibitors. (See **PRECAUTIONS, Drug Interactions.**)

PRECAUTIONS
Monitor for fluid or electrolyte imbalances at appropriate intervals. Do frequent serum and urine electrolyte determinations (especially when the patient is vomiting or receiving parenteral fluids). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy usually is water restriction. In actual salt depletion, appropriate replacement is the therapy of choice.

Hypokalemia may develop with thiazide therapy, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids, ACTH, amphotericin B or after prolonged thiazide therapy.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (eg, increased ventricular irritability).

MAXZIDE may produce an elevated blood urea nitrogen level (BUN), creatinine level, or both. Elevations in BUN and creatinine levels may be more frequent in patients receiving divided dose diuretic therapy. Discontinue if azotemia increases.

Use with caution in patients with impaired hepatic function or progressive liver disease and in patients with histories of renal lithiasis. Triamterene is a weak folic acid antagonist. Periodic blood evaluations are recommended. Hyperuricemia may occur or acute gout may be precipitated in certain patients receiving thiazide therapy. The thiazides may decrease serum PBI level without signs of thyroid disturbance.

Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. Discontinue thiazides before conducting tests for parathyroid function.

Insulin requirements in diabetic patients may be changed. Thiazides may cause manifestation of latent diabetes mellitus. Sensitivity reactions to thiazides may occur in patients with or

MAXZIDE® and MAXZIDE®-25 MG Tablets
Triamterene and Hydrochlorothiazide

without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus by thiazides has been reported.

Thiazides may add to or potentiate the action of other antihypertensive drugs. Thiazides may decrease arterial responsiveness to norepinephrine. Thiazides have also been shown to increase responsiveness to tubocurarine. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Acute renal failure has been reported in a few patients receiving indomethacin and other formulations containing triamterene and hydrochlorothiazide. Caution is therefore advised when administering nonsteroidal anti-inflammatory agents with MAXZIDE.

Use potassium-sparing agents very cautiously, if at all, in conjunction with angiotensin-converting enzyme (ACE) inhibitors due to a greatly increased risk of hyperkalemia. Monitor serum potassium frequently.

MAXZIDE may interfere with quinidine measurement. **Pregnancy Category C:** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, pancreatitis, and possibly other adverse reactions which have occurred in the adult.

Thiazides appear in breast milk. If use is essential, the patient should stop nursing. Adequate information on use in children is not available.

ADVERSE REACTIONS
Side effects observed in association with the use of MAXZIDE, other combination products containing triamterene/hydrochlorothiazide, and products containing triamterene or hydrochlorothiazide include the following:
Gastrointestinal: jaundice (intrahepatic cholestatic jaundice), pancreatitis, nausea, appetite disturbance, taste alteration, vomiting, diarrhea, constipation, anorexia, gastric irritation, cramping. **Central Nervous System:** drowsiness and fatigue, insomnia, headache, dizziness, dry mouth, depression, anxiety, vertigo, restlessness, paresthesias. **Cardiovascular:** tachycardia, shortness of breath and chest pain, orthostatic hypotension (may be aggravated by alcohol, barbiturates or narcotics). **Renal:** acute renal failure, acute interstitial nephritis, renal stones composed of triamterene in association with other calculus materials, urine discoloration. **Hematologic:** leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, hemolytic anemia and megaloblastosis. **Ophthalmic:** xanthopsia, transient blurred vision. **Hypersensitivity:** anaphylaxis, photosensitivity, rash, urticaria, purpura, necrotizing angiitis (vasculitis, cutaneous vasculitis), fever, respiratory distress including pneumonitis. **Other:** muscle cramps and weakness, decreased sexual performance and sialadenitis. Whenever adverse reactions are moderate to severe, therapy should be reduced or withdrawn. **Altered Laboratory Findings: Serum Electrolytes:** hyperkalemia, hypokalemia, hyponatremia, hypomagnesemia, hypochloremia (see **WARNINGS, PRECAUTIONS**). **Creatinine, Blood Urea Nitrogen:** Reversible elevations in BUN and serum creatinine have been observed in hypertensive patients treated with MAXZIDE. **Glucose:** hyperglycemia, glycosuria and diabetes mellitus (see **PRECAUTIONS**). **Serum Uric Acid, PBI and Calcium:** (see **PRECAUTIONS**). **Other:** Elevated liver enzymes have been reported in patients receiving MAXZIDE.

Rev. 3/90
23025

References
1. Schnaper HW, Maxwell MH. Efficacy and safety of triamterene/hydrochlorothiazide combinations in mild systemic hypertension. *Am J Cardiol.* 1989;63:32B-36B.
2. Data on file, Lederle Laboratories, Pearl River, NY.
3. *Physicians' Desk Reference®* 46th ed. Montvale, NJ: Medical Economics Data; 1992:1215

LEDERLE LABORATORIES
A Division of American Cyanamid Company
Wayne, New Jersey 07470

June 1992

8504-21

NIZORAL® *(ketoconazole) 2% Cream*

Before prescribing please consult complete prescribing information, of which the following is a brief summary.

MICROBIOLOGY: Ketoconazole is a broad spectrum synthetic antifungal agent which inhibits the *in vitro* growth of the following common dermatophytes and yeasts by altering the permeability of the cell membrane: dermatophytes: *Trichophyton rubrum, T. mentagrophytes, T. tonsurans, Microsporum canis, M. audouini, M. gypseum* and *Epidermophyton floccosum;* yeasts: *Candida albicans, Malassezia ovale (Pityrosporum ovale)* and *C. tropicalis;* and the organism responsible for tinea versicolor, *Malassezia furfur (Pityrosporum orbiculare).* Only those organisms listed in the INDICATIONS AND USAGE Section have been proven to be clinically affected. Development of resistance to ketoconazole has not been reported.

INDICATIONS AND USAGE: NIZORAL® (ketoconazole) 2% Cream is indicated for the topical treatment of tinea corporis and tinea cruris caused by *Trichophyton rubrum, T. mentagrophytes** and *Epidermophyton floccosum;* in the treatment of tinea (pityriasis) versicolor caused by *Malassezia furfur (Pityrosporum orbiculare);* in the treatment of cutaneous candidiasis caused by *Candida spp.* and in the treatment of seborrheic dermatitis.

*Efficacy for this organism in this organ system was studied in fewer than ten infections.

CONTRAINDICATIONS: NIZORAL® (ketoconazole) 2% Cream is contraindicated in persons who have shown hypersensitivity to the active or excipient ingredients of this formulation.

WARNINGS: NIZORAL® (ketoconazole) 2% Cream is not for ophthalmic use.

NIZORAL® (ketoconazole) 2% Cream contains sodium sulfite anhydrous, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

PRECAUTIONS: General: If a reaction suggesting sensitivity or chemical irritation should occur, use of the medication should be discontinued. Hepatitis (1:10,000 reported incidence) and, at high doses, lowered testosterone and ACTH induced corticosteroid serum levels have been seen with orally administered ketoconazole; these effects have not been seen with topical ketoconazole.

Carcinogenesis, Mutagenesis, Impairment of Fertility: A long-term feeding study in Swiss Albino mice and in Wistar rats showed no evidence of oncogenic activity. The dominant lethal mutation test in male and female mice revealed that single oral doses of ketoconazole as high as 80 mg/kg produced no mutation in any stage of germ cell development. The Ames' *Salmonella* microsomal activator assay was also negative.

Pregnancy: Teratogenic effects: Pregnancy Category C: Ketoconazole has been shown to be teratogenic (syndactylia and oligodactylia) in the rat when given orally in the diet at 80 mg/kg/day, (10 times the maximum recommended human oral dose). However, these effects may be related to maternal toxicity, which was seen at this and higher dose levels.

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

Nursing Mothers: It is not known whether NIZORAL® (ketoconazole) 2% Cream administered topically could result in sufficient systemic absorption to produce detectable quantities in breast milk. Nevertheless, a decision should be made whether to discontinue nursing or 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: During clinical trials 45 (5.0%) of 905 patients treated with NIZORAL® (ketoconazole) 2% Cream and 5 (2.4%) of 208 patients treated with placebo reported side effects consisting mainly of severe irritation, pruritus and stinging. One of the patients treated with NIZORAL® Cream developed a painful allergic reaction.

DOSAGE AND ADMINISTRATION: *Cutaneous candidiasis, tinea corporis, tinea cruris, and tinea (pityriasis) versicolor:* It is recommended that NIZORAL® (ketoconazole) 2% Cream be applied once daily to cover the affected and immediate surrounding area. Clinical improvement may be seen fairly soon after treatment is begun; however, candidal infections and tinea cruris and corporis should be treated for two weeks in order to reduce the possibility of recurrence. Patients with tinea versicolor usually require two weeks of treatment.

Seborrheic dermatitis: NIZORAL® (ketoconazole) 2% Cream should be applied to the affected area twice daily for four weeks or until clinical clearing.

If a patient shows no clinical improvement after the treatment period, the diagnosis should be redetermined.

Manufactured by: ALTANA, INC., Melville, N.Y. 11747
Revised Nov. 1987, Feb. 1988 U.S. Patent No. 4,335,125 1P41J98G-M

NIZORAL® *(ketoconazole) Tablets*

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

WARNING: Ketoconazole has been associated with hepatic toxicity, including some fatalities. Patients receiving this drug should be informed by the physician of the risk and should be closely monitored. See WARNINGS and PRECAUTIONS sections.

CLINICAL PHARMACOLOGY: NIZORAL is active against clinical infections with *Blastomyces dermatitidis, Candida spp., Coccidioides immitis, Histoplasma capsulatum, Paracoccidioides brasiliensis,* and *Phialophora spp.* It is also active against *Trichophyton spp., Epidermophyton spp.,* and *Microsporum spp.* NIZORAL is active *in vitro* against a variety of fungi and yeast. In animal models, activity has been demonstrated against *Candida spp., Blastomyces dermatitidis, Histoplasma capsulatum, Malassezia furfur, Coccidioides immitis,* and *Cryptococcus neoformans.*

INDICATIONS AND USAGE: NIZORAL (ketoconazole) is indicated for the treatment of the following systemic fungal infections: candidiasis, chronic mucocutaneous candidiasis, oral thrush, candiduria, blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis. NIZORAL should not be used for fungal meningitis because it penetrates poorly into the cerebral-spinal fluid.

NIZORAL is also indicated for the treatment of patients with severe recalcitrant cutaneous dermatophyte infections who have not responded to topical therapy or oral griseofulvin, or who are unable to take griseofulvin.

CONTRAINDICATIONS: NIZORAL is contraindicated in patients who have shown hypersensitivity to the drug.

WARNINGS: Hepatotoxicity, primarily of the hepatocellular type, has been associated with the use of NIZORAL (ketoconazole), including rare fatalities. The reported incidence of hepatotoxicity has been about 1:10,000 exposed patients, but this probably represents some degree of under-reporting, as is the case for most reported adverse reactions to drugs. The median duration of ketoconazole therapy in patients who developed symptomatic hepatotoxicity was about 28 days, although the range extended to as low as 3 days. The hepatic injury has usually, but not always, been reversible upon discontinuation of NIZORAL (ketoconazole) treatment. Several cases of hepatitis have been reported in children.

Prompt recognition of liver injury is essential. Liver function tests (such as SGGT, alkaline phosphatase, SGPT, SGOT and bilirubin) should be measured before starting treatment and at frequent intervals during treatment. Patients receiving ketoconazole concurrently with other potentially hepatotoxic drugs should be carefully monitored, particularly those patients requiring prolonged therapy or those who have had a history of liver disease.

Most of the reported cases of hepatic toxicity have to date been in patients treated for onychomycosis. Of 180 patients worldwide developing idiosyncratic liver dysfunction during ketoconazole therapy, 61.3% had onychomycosis and 16.8% had chronic recalcitrant dermatophytoses.

Transient minor elevations in liver enzymes have occurred during ketoconazole treatment. The drug should be discontinued if these persist, if the abnormalities worsen, or if the abnormalities become accompanied by symptoms of possible liver injury.

In rare cases anaphylaxis has been reported after the first dose. Several cases of hypersensitivity reactions including urticaria have also been reported.

In European clinical trials involving 350 patients with metastatic prostatic cancer, eleven deaths were reported within two weeks of starting treatment with high doses of ketoconazole (1200 mg/day). It is not possible to ascertain from the information available whether death was related to ketoconazole therapy in these patients with serious underlying disease. However, high doses of ketoconazole are known to suppress adrenal corticosteroid secretion.

In female rats treated three to six months with ketoconazole at dose levels of 80 mg/kg and higher, increased fragility of long bones, in some cases leading to fracture, was seen. The maximum "no-effect" dose level in these studies was 20 mg/kg (2.5 times the maximum recommended human dose). The mechanism responsible for this phenomenon is obscure. Limited studies in dogs failed to demonstrate such an effect on the metacarpals and ribs.

PRECAUTIONS: *General:* NIZORAL (ketoconazole) has been demonstrated to lower serum testosterone. Once therapy with NIZORAL has been discontinued, serum testosterone levels return to baseline values. Testosterone levels are impaired with doses of 800 mg per day and abolished by 1600 mg per day. NIZORAL also decreases ACTH induced corticosteroid serum levels at similar high doses. The recommended dose of 200 mg - 400 mg daily should be followed closely.

In four subjects with drug-induced achlorhydria, a marked reduction in NIZORAL absorption was observed. NIZORAL requires acidity for dissolution. If concomitant antacids, anticholinergics, and H_2-blockers are needed, they should be given at least two hours after NIZORAL administration. In cases of achlorhydria, the patients should be instructed to dissolve each tablet in 4 ml aqueous solution of 0.2 N HCl. For ingesting the resulting mixture, they should use a drinking straw so as to avoid contact with the teeth. This administration should be followed with a cup of tap water.

Information for Patients: Patients should be instructed to report any signs and symptoms which may suggest liver dysfunction so that appropriate biochemical testing can be done. Such signs and symptoms may include unusual fatigue, anorexia, nausea and/or vomiting, jaundice, dark urine or pale stools (see WARNINGS).

Drug Interactions: Imidazole compounds like ketoconazole may enhance the anticoagulant effect of coumarin-like drugs. In simultaneous treatment with imidazole drugs and coumarin drugs, the anticoagulant effect should be carefully titrated and monitored.

Concomitant administration of rifampin with ketoconazole reduces the blood levels of the latter. INH (Isoniazid) is also reported to affect ketoconazole concentrations adversely. These drugs should not be given concomitantly.

Ketoconazole increases the blood level of cyclosporin A. Blood levels of cyclosporin A should be monitored if the two drugs are given concomitantly.

Concomitant administration of ketoconazole with phenytoin may alter the metabolism of one or both of the drugs. It is suggested to monitor both ketoconazole and phenytoin.

Because severe hypoglycemia has been reported in patients concomitantly receiving oral miconazole (an imidazole) and oral hypoglycemic agents, such a potential interaction involving the latter agents when used concomitantly with ketoconazole (an imidazole) can not be ruled out.

Preliminary evidence shows that ketoconazole inhibits the metabolism of terfenadine, resulting in an increased plasma concentration of terfenadine and a delay in the elimination of its acid metabolite. Increased plasma concentration of terfenadine or its acid metabolite may result in prolonged QT intervals. Cases of torsades de pointes and other ventricular dysrhythmias have been reported in patients taking terfenadine concurrently with ketoconazole. Concurrent administration of terfenadine with ketoconazole is not recommended.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The dominant lethal mutation test in male and female mice revealed that single oral doses of NIZORAL as high as 80 mg/kg produced no mutation in any stage of germ cell development. The *Ames Salmonella* microsomal activator assay was also negative. A long term feeding study in Swiss Albino mice and in Wistar rats showed no evidence of oncogenic activity.

Pregnancy: Teratogenic effects: *Pregnancy Category C.* NIZORAL (ketoconazole) has been shown to be teratogenic (syndactylia and oligodactylia) in the rat when given in the diet at 80 mg/kg/day, (10 times the maximum recommended human dose). However, these effects may be related to maternal toxicity, evidence of which also was seen at this and higher dose levels.

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

Nonteratogenic effects: NIZORAL has also been found to be embryotoxic in the rat when given in the diet at doses higher than 80 mg/kg during the first trimester of gestation.

In addition, dystocia (difficult labor) was noted in rats administered NIZORAL during the third trimester of gestation. This occurred when NIZORAL was administered at doses higher than 10 mg/kg (higher than 1.25 times the maximum human dose).

It is likely that both the malformations and the embryotoxicity resulting from the administration of NIZORAL (ketoconazole) during gestation are a reflection of the particular sensitivity of the female rat to this drug. For example, the oral LD'_{50} of NIZORAL given by gavage to the female rat is 166 mg/kg whereas in the male rat the oral LD_{50} is 287 mg/kg.

Nursing Mothers: Since NIZORAL is probably excreted in the milk, mothers who are under treatment should not breast feed.

Pediatric Use: NIZORAL has not been systematically studied in children of any age, and essentially no information is available on children under 2 years. NIZORAL should not be used in pediatric patients unless the potential benefit outweighs the risks.

ADVERSE REACTIONS: In rare cases, anaphylaxis has been reported after the first dose. Several cases of hypersensitivity reactions including urticaria have also been reported. However, the most frequent adverse reactions were nausea and/or vomiting in approximately 3%, abdominal pain in 1.2%, pruritus in 1.5%, and the following in less than 1% of the patients: headache, dizziness, somnolence, fever and chills, photophobia, diarrhea, gynecomastia, impotence, thrombocytopenia, leukopenia, hemolytic anemia, and bulging fontanelles. Oligospermia has been reported in investigational studies with the drug at dosages above those currently approved. Although oligospermia has not been reported at dosages up to 400 mg daily, sperm counts have been obtained infrequently in patients treated with these dosages. Most of these reactions were mild and transient and rarely required discontinuation of NIZORAL. In contrast, the rare occurrences of hepatic dysfunction require special attention (see WARNINGS).

Neuropsychiatric disturbances, including suicidal tendencies and severe depression, have occurred rarely in patients using NIZORAL.

OVERDOSAGE: In the event of accidental overdosage, supportive measures, including gastric lavage with sodium bicarbonate, should be employed.

Rev. March 1989, April 1991 U.S. Patent 4,335,125

NIZORAL® (ketoconazole) 2% Shampoo

Before prescribing, please consult complete prescribing information of which the following is a brief summary.

MICROBIOLOGY: NIZORAL® (ketoconazole) is a broad-spectrum synthetic antifungal agent which inhibits the growth of the following common dermatophytes and yeasts by altering the permeability of the cell membrane: dermatophytes: *Trichophyton rubrum, T. mentagrophytes, T. tonsurans, Microsporum canis, M. audouini, M. gypseum* and *Epidermophyton floccosum;* yeasts: *Candida albicans, C. tropicalis, Pityrosporum ovale (Malassezia ovale)* and *Pityrosporum orbiculare (M. furfur).* Development of resistance by these microorganisms to ketoconazole has not been reported.

INDICATIONS AND USAGE: NIZORAL® (ketoconazole) 2% Shampoo is indicated for the reduction of scaling due to dandruff.

CONTRAINDICATIONS: NIZORAL® (ketoconazole) 2% Shampoo is contraindicated in persons who have shown hypersensitivity to the active ingredient or excipients of this formulation.

PRECAUTIONS: General: If a reaction suggesting sensitivity or chemical irritation should occur, use of the medication should be discontinued.

Information for Patients: May be irritating to mucous membranes of the eyes and contact with this area should be avoided.

There have been reports that use of the shampoo resulted in removal of the curl from pemanently waved hair.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The dominant lethal mutation test in male and female mice revealed that single oral doses of ketoconazole as high as 80 mg/kg produced no mutation in any stage of germ cell development. The Ames Salmonella microsomal activator assay was also negative. A long-term feeding study of ketoconazole in Swiss Albino mice and in Wistar rats showed no evidence of oncogenic activity.

Pregnancy: Teratogenic effects: Pregnancy Category C: Ketoconazole is not detected in plasma after chronic shampooing. Ketoconazole has been shown to be teratogenic (syndactylia and oligodactylia) in the rat when given orally in the diet at 80 mg/kg/day (10 times the maximum recommended human oral dose). However, these effects may be related to maternal toxicity, which was seen at this and higher dose levels.

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

Nursing mothers: Ketoconazole is not detected in plasma after chronic shampooing. Nevertheless, caution should be exercised when NIZORAL® (ketoconazole) 2% Shampoo is administered to a nursing woman.

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

ADVERSE REACTIONS: In 11 double-blind trials in 264 patients using ketoconazole 2% shampoo, an increase in normal hair loss and irritation occurred in less than 1% of patients. In three open-label safety trials in which 41 patients shampooed 4-10 times weekly for six months, the following adverse experiences each occurred once: abnormal hair texture, scalp pustules, mild dryness of the skin, and itching. As with other shampoos, oiliness and dryness of hair and scalp have been reported.

OVERDOSAGE: NIZORAL® (ketoconazole) 2% Shampoo is intended for external use only. In the event of ingestion, supportive measures, including gastric lavage with sodium bicarbonate, should be employed.

HOW SUPPLIED: NIZORAL® (ketoconazole) 2% Shampoo is a pink liquid supplied in a 4-fluid ounce nonbreakable plastic bottle (NDC 50458-223-04).

Storage conditions: Store at a temperature not above 25°C (77°F). Protect from light.

Manufactured by: Janssen Pharmaceutica n.v., Beerse, Belgium
Printed June 1990 U.S. Patent No. 4,335,125 7500001-M

Distributed by: Janssen Pharmaceutica Inc., Titusville, NJ 08560

world leader in antimycotic research

JANSSEN · PHARMACEUTICA · RESEARCH FOUNDATION ·

Titusville, NJ 08560-0200

JPI-NZ-066 June 1992 Printed in U.S.A.

Lopressor®

metoprolol tartrate USP

Tablets

Ampuls

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE

Hypertension

Lopressor tablets are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive agents.

Angina Pectoris

Lopressor is indicated in the long-term treatment of angina pectoris.

Myocardial Infarction

Lopressor ampuls and tablets are indicated in the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment with intravenous Lopressor can be initiated as soon as the patient's clinical condition allows (see **DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS,** and **WARNINGS**). Alternatively, treatment can begin within 3 to 10 days of the acute event (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

Hypertension and Angina

Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **WARNINGS**).

Myocardial Infarction

Lopressor is contraindicated in patients with a heart rate < 45 beats/min; second- and third-degree heart block; significant first-degree heart block (P-R interval ≥ 0.24 sec); systolic blood pressure < 100 mmHg; or moderate-to-severe cardiac failure (see **WARNINGS**).

WARNINGS

Hypertension and Angina

Cardiac Failure: Sympathetic stimulation is a vital component 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 hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and Lopressor slow AV conduction.

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 given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, Lopressor should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Lopressor, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Lopressor administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Lopressor therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Lopressor should be used. In these circumstances it would be prudent initially to administer Lopressor in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See DOSAGE AND ADMINISTRATION.)**

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Lopressor, like other beta blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heartbeat has also been reported with beta blockers.

Diabetes and Hypoglycemia: Lopressor 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.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm.

Myocardial Infarction

Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.

During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored. If heart failure occurs or persists despite appropriate treatment, Lopressor should be discontinued.

Bradycardia: Lopressor produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

AV Block: Lopressor slows AV conduction and may produce significant first- (P-R interval ≥ 0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.

If heart block occurs, Lopressor should be discontinued and atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent beta$_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should *not* be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a beta$_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and beta$_2$ agonists may produce serious cardiac arrhythmias.**

PRECAUTIONS

General

Lopressor should be used with caution in patients with impaired hepatic function.

Information for Patients

Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician.

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Lopressor has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Lopressor.

Laboratory Tests

Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

Drug Interactions

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have been conducted to evaluate carcinogenic potential. In a 2-year study in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative.

No evidence of impaired fertility due to Lopressor was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.

Pregnancy Category C

Lopressor has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. 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.

Nursing Mothers

Lopressor is excreted in breast milk in very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Lopressor is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Hypertension and Angina

Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, nightmares, and insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; and hypotension have been reported in about 1 of 100 patients. (See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS.**)

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see **WARNINGS**).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients.

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor.

Myocardial Infarction

Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.

Cardiovascular: In the randomized comparison of Lopressor and placebo described in the CLINICAL PHARMACOLOGY section, the following adverse reactions were reported:

	Lopressor	*Placebo*
Hypotension (systolic BP < 90 mmHg)	27.4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R ≥ 0.26 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.

Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.

Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.

Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.

Potential Adverse Reactions

A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor.

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

Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

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

OVERDOSAGE

Acute Toxicity

Several cases of overdosage have been reported, some leading to death.

Oral LD_{50}'s (mg/kg): mice, 1158-2460; rats, 3090-4670.

Signs and Symptoms

Potential signs and symptoms associated with overdosage with Lopressor are bradycardia, hypotension, bronchospasm, and cardiac failure.

Treatment

There is no specific antidote.

In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly (see **WARNINGS, Myocardial Infarction**).

On the basis of the pharmacologic actions of Lopressor, the following general measures should be employed:

Elimination of the Drug: Gastric lavage should be performed.

Bradycardia: Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.

Hypotension: A vasopressor should be administered, e.g., levarterenol or dopamine.

Bronchospasm: A beta$_2$-stimulating agent and/or a theophylline derivative should be administered.

Cardiac Failure: A digitalis glycoside and diuretic should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered.

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Geigy

GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
Ardsley, New York 10502

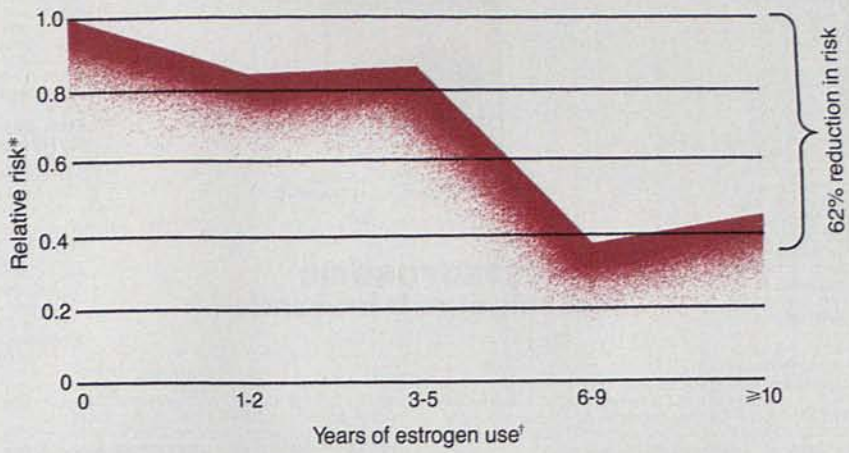
1. 1988 Joint National Committee. The 1988 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med.* 1988;148:1023-1038.


6′
5′
3′
For the woman
at risk...

PREMARIN® 0.625 mg prevents postmenopausal osteoporosis and reduces the risk of hip and wrist fractures by as much as 62%[1]

Start early and continue long-term for maximum osteoporosis benefits

Relative risk of hip and wrist fractures in postmenopausal women according to duration of estrogen therapy



*Standardized for age group (50 to 59, 60 to 69, and 70 to 74 years), history of hysterectomy, and current use versus past use of estrogens
†Includes women using estrogen less than 1 year

Adapted from Weiss et al[1]

Contraindications

Estrogens should not be used in women (or men) with any of the following conditions: known or suspected 1) pregnancy, 2) breast cancer, 3) estrogen-dependent neoplasia, 4) undiagnosed abnormal genital bleeding, 5) active thrombophlebitis or thromboembolic disorders.

Note: Estrogens have been reported to increase the risk of endometrial carcinoma in postmenopausal women.

PREMARIN®
(conjugated estrogens tablets) 0.625 mg

OSTEOPOROSIS
The only cure is prevention

Please see brief summary of prescribing information on next page.

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

PREMARIN® Brand of conjugated estrogens tablets, USP
PREMARIN® Brand of conjugated estrogens Vaginal Cream, in a nonliquefying base

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA. Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures including endometrial sampling when indicated should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is currently no evidence that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.
2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY. Estrogen therapy during pregnancy is associated with an increased risk of congenital defects in the reproductive organs of the male and female fetus, an increased risk of vaginal adenosis, squamous-cell dysplasia of the uterine cervix, and vaginal cancer in the female later in life. The 1985 DES Task Force concluded that women who used DES during their pregnancies may subsequently experience an increased risk of breast cancer. However, a causal relationship is still unproven, and the observed level of risk is similar to that for a number of other breast cancer risk factors.

There is no indication for estrogen therapy during pregnancy. Estrogens are ineffective for the prevention or treatment of threatened or habitual abortion.

DESCRIPTION: PREMARIN (conjugated estrogens, USP) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters. Tablets are available in 0.3 mg, 0.625 mg, 0.9 mg, 1.25 mg, and 2.5 mg strengths of conjugated estrogens. Cream is available as 0.625 mg conjugated estrogens per gram.

INDICATIONS AND USAGE: Moderate-to-severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause and they should not be used to treat these conditions.) Prevention and management of osteoporosis (abnormally low bone mass). Atrophic vaginitis. Atrophic urethritis. Hypoestrogenism due to hypogonadism, castration or primary ovarian failure.

PREMARIN (conjugated estrogens) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae.

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected pregnancy (see Boxed Warning). 2. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 3. Known or suspected estrogen-dependent neoplasia. 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. Estrogen replacement therapy has not been reported to increase the risk of thrombophlebitis and/or thromboembolic disease. However, there is insufficient information regarding women who have had previous thromboembolic disease.

PREMARIN Tablets and Vaginal Cream should not be used in patients hypersensitive to their ingredients.

PREMARIN®
(conjugated estrogens tablets)

The appearance of this tablet is a trademark of Wyeth-Ayerst Laboratories.

OSTEOPOROSIS
The only cure is prevention

WARNINGS: Some studies suggest a possible increased incidence of breast cancer in women taking higher doses of estrogen for prolonged time periods. The majority of studies have not shown an association with usual estrogen replacement doses. Endometrial cancer risk among estrogen users was about 4-fold or greater than in non-users, and appears dependent on treatment duration and estrogen dose. In patients on combined estrogen-progestin therapy, this risk appears to be decreased. (See PRECAUTIONS below.)

Estrogen therapy during pregnancy is associated with an increased risk of fetal congenital reproductive tract disorders.

A 2.5-fold increase in the risk of surgically confirmed gall bladder disease in women receiving postmenopausal estrogens has been reported.

Large doses of estrogen such as those used to treat prostate and breast cancer have been shown to increase the risk of non-fatal myocardial infarction, pulmonary embolism, and thrombophlebitis in men. This cannot necessarily be extrapolated to women. However, to avoid theoretical cardiovascular risk caused by high estrogen doses, the doses for estrogen replacement therapy should not exceed the recommended dose.

Blood pressure should be monitored with estrogen use, especially if high doses are used.

Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: The addition of a progestin for 7 or more days of a cycle of estrogen administration reportedly lowers the incidence of endometrial hyperplasia. Studies of endometrium suggest that 10 to 13 days of progestin are needed to provide maximal endometrial maturation and elimination of hyperplastic changes. Additional risks, such as adverse effects on carbohydrate and lipid metabolism, may be associated with the inclusion of progestin in estrogen replacement regimens. The choice of progestin and dosage may be important in minimizing these adverse effects.

Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention, such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding and mastodynia. Pre-existing uterine leiomyomata may increase in size during estrogen use. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, or metabolic bone diseases associated with hypercalcemia.

The following drug/laboratory test interactions have been reported, some only with estrogen-progestin combinations (oral contraceptives):

1. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
2. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by T_4 levels determined by column or by radioimmunoassay. Free T_3 resin uptake is decreased, reflecting the elevated TBG; free T_4 concentration is unaltered.
3. Impaired glucose tolerance.
4. Reduced response to metyrapone test.
5. Reduced serum folate concentration.

MUTAGENESIS AND CARCINOGENESIS: Long-term, continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver.

PREGNANCY CATEGORY X: Estrogens should not be used during pregnancy. See **CONTRAINDICATIONS** and Boxed Warning.

NURSING MOTHERS: As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy: changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow, breakthrough bleeding, spotting, increase in size of uterine fibromyomata, vaginal candidiasis, change in amount of cervical secretion; tenderness or enlargement of breasts; nausea, vomiting, abdominal cramps, bloating, cholestatic jaundice; chloasma or melasma that may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism; steepening of corneal curvature, intolerance to contact lenses; headache, migraine, dizziness, mental depression, chorea; increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

ACUTE OVERDOSAGE: May cause nausea and vomiting.

DOSAGE AND ADMINISTRATION:

PREMARIN® Brand of conjugated estrogens tablets, USP

1. *Given cyclically for short-term use only.* For treatment of moderate-to-severe vasomotor symptoms, atrophic vaginitis, or atrophic urethritis associated with the menopause (0.3 mg to 1.25 mg or more daily). The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible. Administration should be cyclic (eg, three weeks on and one week off). Attempts to discontinue or taper medication should be made at three- to six-month intervals.
2. *Given cyclically:* Hypoestrogenism. Osteoporosis.

Hypoestrogenism due to: Female hypogonadism—2.5 mg to 7.5 mg daily in divided doses for 20 days followed by 10 day rest period. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. Female castration or primary ovarian failure—1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis—0.625 mg daily. Administration should be cyclic (eg, three weeks on and one week off).

PREMARIN® Brand of conjugated estrogens Vaginal Cream

Given cyclically for short-term use only. For treatment of atrophic vaginitis or kraurosis vulvae.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Attempts to discontinue or taper medication should be made at three- to six-month intervals.

Usual dosage range: 2 g to 4 g daily, intravaginally, depending on the severity of the condition.

Patients with an intact uterus who are treated with either PREMARIN Tablets or Vaginal Cream should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

Revised August 21, 1989

70662R

Reference:
1. Weiss NS, Ure CL, Ballard JH, et al: Decreased risk of fractures of the hip and lower forearm with postmenopausal use of estrogen. *N Engl J Med* 1980;303:1195-1198.

Worldwide Leadership in Female Healthcare

WYETH-AYERST LABORATORIES
Philadelphia, PA 19101

TWO LANDMARK STUDIES,[1,2]
PRESENTED AT THE
1992 AMERICAN COLLEGE OF
CARDIOLOGY MEETING,

FINALLY RESOLVED

A 200-YEAR-OLD CONTROVERSY...

LANOXIN IS EFFECTIVE IN CONGESTIVE HEART FAILURE PATIENTS IN NORMAL SINUS RHYTHM, WITH OR WITHOUT AN ACE INHIBITOR.[1,2*†]

*The RADIANCE—Randomized Assessment of Digoxin on Inhibitors of the ANgiotensin Converting Enzyme—study was a multicenter, randomized, double-blind, placebo-controlled study of digoxin in CHF patients receiving diuretics *and* ACE inhibitors.

†The PROVED—Prospective Randomized study of Ventricular failure and the Efficacy of Digoxin—study was a multicenter, randomized, double-blind, placebo-controlled study of digoxin in CHF patients receiving diuretics.

In early CHF.

LANOXIN®
(digoxin) Tablets
125 µg (0.125 mg)
250 µg (0.25 mg)
500 µg (0.5 mg)

EFFECTIVE THERAPY... WITH OR WITHOUT AN ACE INHIBITOR.

Please see brief summary of prescribing information below.

LANOXIN® (DIGOXIN) TABLETS

Before prescribing, physicians should be thoroughly familiar with all aspects of this cardiac (or digitalis) glycoside as discussed in the full prescribing information.

Brief Summary

CONTRAINDICATIONS:
(1) ventricular fibrillation, (2) an untoward effect requiring discontinuation of other digitalis preparations, and (3) a hypersensitivity or allergy to digoxin.

WARNINGS: The use of digoxin for the treatment of obesity is dangerous since it may cause potentially fatal arrhythmias. Anorexia, nausea, vomiting and arrhythmias may be indications of digitalis toxicity; if so, digoxin should be temporarily withheld when possible. Patients with renal insufficiency require smaller than usual maintenance doses of digoxin. Heart failure accompanying acute glomerulonephritis requires extreme care in digitalization and careful monitoring. Relatively low loading and maintenance doses and concomitant use of antihypertensive drugs may be necessary. Digoxin should be discontinued as soon as possible in this setting. Patients with severe carditis are especially sensitive to digoxin-induced rhythm disturbances. Newborn infants display considerable variability in their tolerance to digoxin with premature and immature infants being particularly sensitive; reduce and individualize dosage accordingly. Note: Digoxin is an important cause of accidental poisoning in children.

PRECAUTIONS: Digoxin toxicity develops more frequently and lasts longer in patients with renal impairment because of the decreased excretion of digoxin. Normal potassium and magnesium levels should be maintained in patients treated with digoxin. Calcium, particularly when administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. Hypercalcemia predisposes the patient to digitalis toxicity, whereas hypocalcemia can cause digoxin to become ineffective. Patients with acute myocardial infarction or severe pulmonary disease may be unusually sensitive to digoxin-induced rhythm disturbances. Atrial arrhythmias associated with hypermetabolic states are particularly resistant to digoxin treatment. Large doses of digoxin are not recommended as the only treatment of these arrhythmias; if large doses are required, be careful to avoid toxicity. In hypothyroidism, digoxin requirements are reduced. Reduction of digoxin dosage may be desirable before electrical cardioversion to avoid induction of ventricular arrhythmias. If digitalis toxicity is suspected, elective cardioversion should be delayed. Patients with incomplete AV blocks may progress to advanced or complete heart block when given digoxin, especially in patients with Stokes-Adams attacks. Digoxin may worsen sinus bradycardia or sinoatrial block in patients with sinus node disease. Digoxin may cause rapid ventricular rates and ventricular fibrillation in patients with Wolff-Parkinson-White Syndrome and atrial fibrillation. Because it may worsen the outflow obstruction in patients with idiopathic hypertrophic subaortic stenosis (IHSS), digoxin should only be used in severe cardiac failure in this setting. Patients with chronic constrictive pericarditis may fail to respond to digoxin. Slowing of the heart rate by digoxin in some patients may further decrease cardiac output. Patients with heart failure from amyloid heart disease or constrictive cardiomyopathies respond poorly to digoxin. (See DRUG INTERACTIONS section.)

Laboratory Tests: Serum electrolytes and renal function should be assessed periodically.

Drug Interactions: Potassium-depleting *corticosteroids* and *diuretics* may be major contributing factors to digitalis toxicity. *Calcium*, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. *Quinidine*, *verapamil*, *amiodarone*, and *propafenone* cause a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. Certain *antibiotics* increase digoxin absorption in patients who inactivate digoxin by bacterial metabolism in the lower intestine, so that digitalis intoxication may result. *Propantheline* and *diphenoxylate*, by decreasing gut motility, may increase digoxin absorption. *Antacids*, *kaolin-pectin*, *sulfasalazine*, *neomycin*, *cholestyramine*, certain *anticancer drugs* and *metoclopramide* may reduce intestinal digoxin absorption, resulting in unexpectedly low serum concentrations. There have been inconsistent reports regarding the effects of other drugs on the serum digoxin concentration. *Thyroid* administration to a digitalized, hypothyroid patient may increase the dose requirement of digoxin. Concomitant use of digoxin and *sympathomimetics* increases the risk of cardiac arrhythmias because both enhance ectopic pacemaker activity. *Succinylcholine* may cause a sudden extrusion of potassium from muscle cells, and may thereby cause arrhythmias in digitalized patients. Although β adrenergic blockers or calcium channel blockers and digoxin may be useful in combination to control atrial fibrillation, their additive effects on AV node conduction can result in complete heart block.

Carcinogenesis: No long-term animal studies have been performed to evaluate carcinogenic potential.

Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with digoxin. Digoxin should only be given to a pregnant woman if clearly needed.

Nursing Mothers: Studies have shown that the digoxin concentration in the mother's milk is far below the usual infant maintenance dose and should have no pharmacologic effect upon the infant. Nevertheless, caution should be exercised when digoxin is administered to a nursing woman.

ADVERSE REACTIONS: The overall incidence of adverse reactions has been reported as 5 to 20%, with 15 to 20% (1 to 4% of all patients) of them being considered serious. Evidence suggests that the incidence of toxicity has decreased since the introduction of the serum digoxin assay and improved standardization of digoxin tablets. Cardiac toxicity accounts for about one-half, gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these adverse reactions.

Adults: ***Cardiac***—unifocal or multiform VPCs; ventricular tachycardia, AV dissociation, accelerated junctional (nodal) rhythm and atrial tachycardia with block; excessive slowing of the pulse, AV block (Wenckebach) of increasing degree may proceed to complete heart block.

Gastrointestinal: anorexia, nausea, vomiting, occasionally diarrhea, and very rarely hemorrhagic necrosis of the intestines and abdominal pain.

CNS: visual disturbances, headache, weakness, dizziness, apathy and psychosis.

Other: gynecomastia.

Infants and Children: Anorexia, nausea, vomiting, diarrhea and CNS disturbances may be present but are rare as initial symptoms in infants. Cardiac arrhythmias are more reliable signs of toxicity. Digoxin in children may produce any arrhythmia. Most common are conduction disturbances or SVTs, such as atrial tachycardia with or without block, and junctional (nodal) tachycardia. Ventricular arrhythmias are less common. Sinus bradycardia may also be a sign of impending digoxin toxicity, especially in infants, even in the absence of first degree heart block.

September 1991 542253

PLEASE CONSULT FULL PRODUCT INFORMATION BEFORE PRESCRIBING

References: 1. Packer M, Gheorghiade M, Young JB, et al. Randomized, double-blind, placebo-controlled, withdrawal study of digoxin in patients with chronic heart failure treated with converting-enzyme inhibitors. *J Am Coll Cardiol*. 1992;19:260A. Abstract. **2.** Young JB, Uretsky BF, Shahidi FE, Yellen LG, Harrison MC, Jolly MK. Multicenter, double-blind, placebo-controlled randomized withdrawal trial of the efficacy and safety of digoxin in patients with mild to moderate chronic heart failure not treated with converting enzyme inhibitors. *J Am Coll Cardiol*. 1992;19:259A. Abstract.

Wellcome

Burroughs Wellcome Co.
Research Triangle Park, NC 27709

Brief Summary of
Prescribing Information as of January 1992

NICODERM®
(nicotine transdermal system)

Systemic delivery of 21, 14, or 7 mg/day over 24 hours

Caution: Federal law prohibits dispensing without prescription.

DESCRIPTION

NICODERM is a transdermal system that provides systemic delivery of nicotine for 24 hours following its application to intact skin.

The NICODERM system is a multilayered rectangular film containing nicotine as the active agent. For the three doses the composition per unit area is identical. Proceeding from the visible surface toward the surface attached to the skin are (1) an occlusive backing (polyethylene/aluminum/polyester/ethylene-vinyl acetate copolymer); (2) a drug reservoir containing nicotine (in an ethylene-vinyl acetate copolymer matrix); (3) a rate-controlling membrane (polyethylene); (4) a polyisobutylene adhesive; and (5) a protective liner that covers the adhesive layer and must be removed before application to the skin.

INDICATIONS AND USAGE

NICODERM treatment is indicated as an aid to smoking cessation for the relief of nicotine withdrawal symptoms. NICODERM treatment should be used as part of a comprehensive behavioral smoking-cessation program.

The use of NICODERM systems for longer than 3 months has not been studied.

CONTRAINDICATIONS

Use of NICODERM systems is contraindicated in patients with hypersensitivity or allergy to nicotine or to any of the components of the therapeutic system.

WARNINGS

Nicotine from any source can be toxic and addictive. Smoking causes lung cancer, heart disease, and emphysema and may adversely affect the fetus and the pregnant woman. For any smoker, with or without concomitant disease or pregnancy, the risk of nicotine replacement in a smoking-cessation program should be weighed against the hazard of continued smoking while using NICODERM systems and the likelihood of achieving cessation of smoking without nicotine replacement.

Pregnancy Warning

Tobacco smoke, which has been shown to be harmful to the fetus, contains nicotine, hydrogen cyanide, and carbon monoxide. Nicotine has been shown in animal studies to cause fetal harm. It is therefore presumed that NICODERM systems can cause fetal harm when administered to a pregnant woman. The effect of nicotine delivery by NICODERM systems has not been examined in pregnancy (see PRECAUTIONS).

Therefore pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before using pharmacological approaches. If NICODERM systems are used during pregnancy, or if the patient becomes pregnant while using NICODERM systems, the patient should be apprised of the potential hazard to the fetus.

Safety Note Concerning Children

The amounts of nicotine that are tolerated by adult smokers can produce symptoms of poisoning and could prove fatal if the NICODERM system is applied or ingested by children or pets. Used 21 mg/day systems contain about 73% (83 mg) of their initial drug content. Therefore, patients should be cautioned to keep both the used and unused NICODERM systems out of the reach of children and pets.

PRECAUTIONS

The patient should be urged to stop smoking completely when initiating NICODERM therapy (see DOSAGE AND ADMINISTRATION). Patients should be informed that if they continue to smoke while using NICODERM systems, they may experience adverse effects due to peak nicotine levels higher than those experienced from smoking alone. If there is a clinically significant increase in cardiovascular or other effects attributable to nicotine, the NICODERM dose should be reduced or NICODERM treatment discontinued (see WARNINGS). Physicians should anticipate that concomitant medications may need dosage adjustment (see Drug Interactions).

The use of NICODERM systems beyond 3 months by patients who stop smoking should be discouraged, because the chronic consumption of nicotine by any route can be harmful and addicting.

Allergic Reactions

In a 6-week, open-label, dermal irritation and sensitization study of NICODERM systems, 7 of 230 patients exhibited definite erythema at 24 hours after application. Upon rechallenge, 4 patients exhibited mild to moderate contact allergy. Patients with contact sensitization should be cautioned that a serious reaction could occur from exposure to other nicotine-containing products or smoking. In the efficacy trials, erythema following system removal was typically seen in about 14% of patients, some edema in 3%, and dropouts due to skin reactions occurred in 2% of patients.

Patients should be instructed to promptly discontinue the use of NICODERM systems and contact their physicians, if they experience severe or persistent local skin reactions (eg, severe erythema, pruritus, or edema) at the site of application or a generalized skin reaction (eg, urticaria, hives, or generalized rash).

Patients using NICODERM therapy concurrently with other transdermal products may exhibit local reactions at both application sites. Reactions were seen in 2 of 7 patients using concomitant Estraderm® (estradiol transdermal system) in clinical trials. In such patients, use of one or both systems may have to be discontinued.

Skin Disease

NICODERM systems are usually well tolerated by patients with normal skin, but may be irritating for patients with some skin disorders (atopic or eczematous dermatitis).

Cardiovascular or Peripheral Vascular Diseases

The risks of nicotine replacement in patients with certain cardiovascular and peripheral vascular diseases should be weighed against the benefits of including nicotine replacement in a smoking-cessation program for them. Specifically, patients with coronary heart disease (history of myocardial infarction and/or angina pectoris), serious cardiac arrhythmias, or vasospastic diseases (Buerger's disease, Prinzmetal's variant angina) should be carefully screened and evaluated before nicotine replacement is prescribed.

Tachycardia occurring in association with the use of NICODERM therapy was reported occasionally. If serious cardiovascular symptoms occur with the use of NICODERM therapy, it should be discontinued.

NICODERM therapy was as well tolerated as placebo in a controlled trial in patients with coronary artery disease (see CLINICAL STUDIES). One patient on NICODERM 21mg/day, two on NICODERM 14 mg/day, and eight on placebo discontinued treatment due to adverse events.

NICODERM therapy did not affect angina frequency or the appearance of arrhythmias on Holter monitoring in these patients.

NICODERM therapy generally should not be used in patients during the immediate post-myocardial infarction period, patients with serious arrhythmias, and patients with severe or worsening angina pectoris.

Renal or Hepatic Insufficiency

The pharmacokinetics of nicotine have not been studied in the elderly or in patients with renal or hepatic impairment. However, given that nicotine is extensively metabolized and that its total system clearance is dependent on liver blood flow, some influence of hepatic impairment on drug kinetics (reduced clearance) should be anticipated. Only severe renal impairment would be expected to affect the clearance of nicotine or its metabolites from the circulation (see Pharmacokinetics).

Endocrine Diseases

NICODERM therapy should be used with caution in patients with hyperthyroidism, pheochromocytoma, or insulin-dependent diabetes, since nicotine causes the release of catecholamines by the adrenal medulla.

Peptic Ulcer Disease

Nicotine delays healing in peptic ulcer disease; therefore, NICODERM therapy should be used with caution in patients with active peptic ulcers and only when the benefits of including nicotine replacement in a smoking-cessation program outweigh the risks.

Accelerated Hypertension

Nicotine therapy constitutes a risk factor for development of malignant hypertension in patients with accelerated hypertension; therefore, NICODERM therapy should be used with caution in these patients and only when the benefits of including nicotine replacement in a smoking-cessation program outweigh the risks.

Information for Patient

A patient instruction booklet is included in the package of NICODERM systems dispensed to the patient. The instruction sheet contains important information and instructions on how to properly use and dispose of NICODERM systems. Patients should be encouraged to ask questions of the physician and pharmacist.

Patients must be advised to keep both used and unused systems out of the reach of children and pets.

Drug Interactions

Smoking cessation, with or without nicotine replacement, may alter the pharmacokinetics of certain concomitant medications.

May Require a Decrease in Dose at Cessation of Smoking	Possible Mechanism
acetaminophen, caffeine, imipramine, oxazepam, pentazocine, propranolol, theophylline	Deinduction of hepatic enzymes on smoking cessation.
insulin	Increase in subcutaneous insulin absorption with smoking cessation.
adrenergic antagonists (eg, prazosin, labetalol)	Decrease in circulating catecholamines with smoking cessation.
May Require an Increase in Dose at Cessation of Smoking	**Possible Mechanism**
adrenergic agonists (eg, isoproterenol, phenylephrine)	Decrease in circulating catecholamines with smoking cessation.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Nicotine itself does not appear to be a carcinogen in laboratory animals. However, nicotine and its metabolites increased the incidences of tumors in the cheek pouches of hamsters and forestomach of F344 rats, respectively, when given in combination with tumor initiators. One study, which could not be replicated, suggested that cotinine, the primary metabolite of nicotine, may cause lymphoreticular sarcoma in the large intestine in rats.

Nicotine and cotinine were not mutagenic in the Ames *Salmonella* test. Nicotine induced repairable DNA damage in an *E. coli* test system. Nicotine was shown to be genotoxic in a test system using Chinese hamster ovary cells. In rats and rabbits, implantation can be delayed or inhibited by a reduction in DNA synthesis that appears to be caused by nicotine. Studies have shown a decrease in litter size in rats treated with nicotine during gestation.

Pregnancy

Pregnancy Category D (see WARNINGS).

The harmful effects of cigarette smoking on maternal and fetal health are clearly established. These include low birth weight, increased risk of spontaneous abortion, and increased perinatal mortality. The specific effects of NICODERM therapy on fetal development are unknown. Therefore pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before using pharmacological approaches.

Spontaneous abortion during nicotine replacement therapy has been reported; as with smoking, nicotine as a contributing factor cannot be excluded.

NICODERM therapy should be used during pregnancy only if the likelihood of smoking cessation justifies the potential risk of use of nicotine replacement by the patient who may continue to smoke.

Teratogenicity

Animal Studies: Nicotine was shown to produce skeletal abnormalities in the offspring of mice when given doses toxic to the dams (25 mg/kg IP or SC).

Human Studies: Nicotine teratogenicity has not been studied in humans except as a component of cigarette smoke (each cigarette smoked delivers about 1 mg of nicotine). It has not been possible to conclude whether cigarette smoking is teratogenic to humans.

Other Effects

Animal Studies: A nicotine bolus (up to 2 mg/kg) to pregnant rhesus monkeys caused acidosis, hypercarbia, and hypotension (fetal and maternal concentrations were about 20 times those achieved after smoking 1 cigarette in 5 minutes). Fetal breathing movements were reduced in the fetal lamb after intravenous injection of 0.25 mg/kg nicotine to the ewe (equivalent to smoking 1 cigarette every 20 seconds for 5 minutes). Uterine blood flow was reduced about 30% after infusion of 0.1 mg/kg/min nicotine for 20 minutes to pregnant rhesus monkeys (equivalent to smoking about 6 cigarettes every minute for 20 minutes).

Human Experience: Cigarette smoking during pregnancy is associated with an increased risk of spontaneous abortion, low birth weight infants, and perinatal mortality. Nicotine and carbon monoxide are considered the most likely mediators of these outcomes. The effect of cigarette smoking on fetal cardiovascular parameters has been studied near term. Cigarettes increased fetal aortic blood flow and heart rate and decreased uterine blood flow and fetal breathing movements. NICODERM therapy has not been studied in pregnant humans.

Labor and Delivery

The NICODERM system is not recommended to be left on during labor and delivery. The effects of nicotine on a mother or the fetus during labor are unknown.

Use in Nursing Mothers

Caution should be exercised when NICODERM therapy is administered to nursing women. The safety of NICODERM therapy in nursing infants has not been examined. Nicotine passes freely into breast milk; the milk to plasma ratio averages 2.9. Nicotine is absorbed orally. An infant has the ability to clear nicotine by hepatic first-pass clearance; however, the efficiency of removal is probably lowest at birth. The nicotine concentrations in milk can be expected to be lower with NICODERM therapy, when used as directed, than with cigarette smoking, as maternal plasma nicotine concentrations are generally reduced with nicotine replacement. The risk of exposure of the infant to nicotine from NICODERM therapy should be weighed against the risks associated with the infant's exposure to nicotine from continued smoking by the mother (passive smoke exposure and contamination of breast milk with other components of tobacco smoke) and from NICODERM therapy alone or in combination with continued smoking.

Pediatric Use

NICODERM therapy is not recommended for use in children, because the safety and effectiveness of NICODERM therapy in children and adolescents who smoke have not been evaluated.

Geriatric Use

Fifty-six patients over the age of 60 participated in clinical trials of NICODERM therapy. NICODERM therapy appeared to be as effective in this age group as in younger smokers. However, asthenia, various body aches, and dizziness occurred slightly more often in patients over 60 years of age.

ADVERSE REACTIONS

Assessment of adverse events in the 1,131 patients who participated in controlled clinical trials is complicated by the occurrence of GI and CNS effects of nicotine withdrawal as well as nicotine excess. The actual incidences of both are confounded by concurrent smoking by many of the patients. When reporting adverse events during the trials, the investigators did not attempt to identify the cause of the symptom.

Topical Adverse Events

The most common adverse event associated with topical nicotine is a short-lived erythema, pruritus, and/or burning at the application site, which was seen at least once in 47% of patients on the NICODERM system in the clinical trials. Local erythema after system removal was noted at least once in 14% of patients and local edema in 3%. Erythema generally resolved within 24 hours. Cutaneous hypersensitivity (contact sensitization) occurred in 2% of patients on NICODERM systems (see PRECAUTIONS, Allergic Reactions).

Probably Causally Related

The following adverse events were reported more frequently in NICODERM-treated patients than in placebo-treated patients or exhibited a dose response in clinical trials.

Digestive System: Diarrhea*, dyspepsia*
Mouth/Tooth Disorders: Dry mouth†
Musculoskeletal System: Arthralgia†, myalgia*
Nervous System: Abnormal dreams*, insomnia (23%), nervousness*
Skin and Appendages: Sweating†

Frequencies for 21 mg/day system
* Reported in 3% to 9% of patients
† Reported in 1% to 3% of patients
Unmarked if reported in <1% of patients

Causal Relationship UNKNOWN

Adverse events reported in NICODERM- and placebo-treated patients at about the same frequency in clinical trials are listed below. The clinical significance of the association between NICODERM systems and these events is unknown, but they are reported as alerting information for the clinician.

Body as a Whole: Asthenia*, back pain*, chest pain†, pain*
Digestive System: Abdominal pain†, constipation*, nausea*, vomiting†
Nervous System: Dizziness*, headache (29%), paresthesia†
Respiratory System: Cough increased*, pharyngitis*, sinusitis†
Skin and Appendages: Rash*
Special Senses: Taste perversion*
Urogenital System: Dysmenorrhea*

Frequencies for 21 mg/day systems
*Reported in 3% to 9% of patients
†Reported in 1% to 3% of patients
Unmarked if reported in <1% of patients

DRUG ABUSE AND DEPENDENCE/TREATMENT OF OVERDOSE

For further information, please see Full Prescribing Information

Manufactured by
ALZA Corporation
Palo Alto, CA 94304 for
Marion Merrell Dow Inc.
Kansas City, MO 64114

Prescribing Information as of January 1992

nidb0192a

MARION MERRELL DOW INC.
KANSAS CITY, MO 64114

For Patients Hit By Cold And Flu

- Unsurpassed efficacy for mild-to-moderate aches and pains vs aspirin[1] and OTC ibuprofen
- Milligram for milligram, as effective as aspirin for fever[2]

EXTRA STRENGTH
TYLENOL®
acetaminophen
500 mg GELCAPS

- Superior GI safety profile to aspirin and even OTC ibuprofen
- Effective in reducing local symptoms, such as arm soreness, associated with influenza vaccine[3]

1000 mg, The most effective dose of TYLENOL®

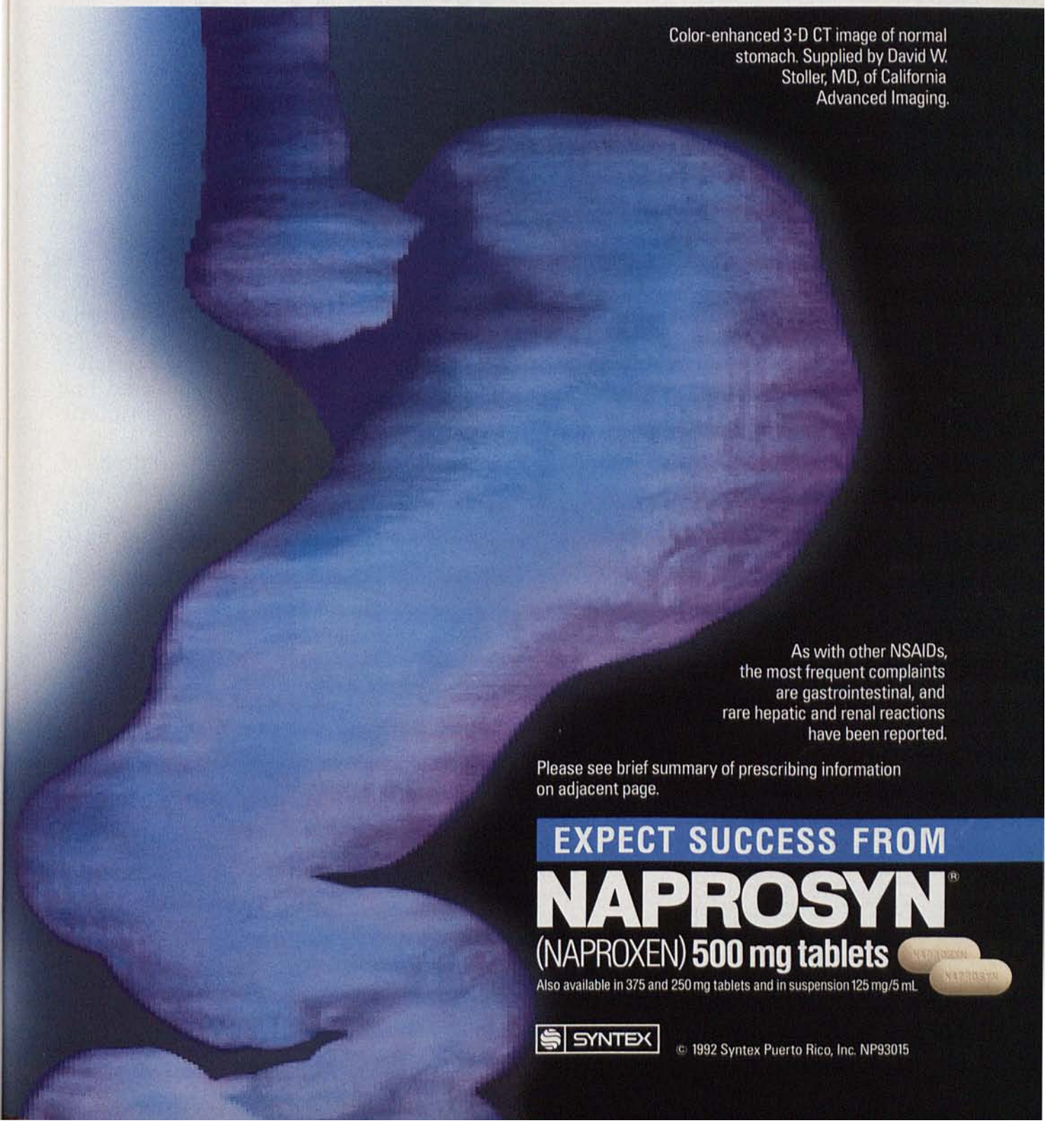
References: 1. Mehlisch DR et al. *Clin Ther.* 1984;7:89-97.
2. Aspirin or paracetamol? *Lancet.* 1981;II:287-289.
3. Yassi A et al. *Clin Invest Med.* 1991;14(suppl 4):A76. Abstract.

McNEIL McNeil Consumer Products Company
Division of McNeil-PPC, Inc.
 Fort Washington, PA 19034 U.S.A.

Do not exceed eight Gelcaps per 24-hour period. Acetaminophen in large overdoses can cause serious adverse effects. In the event of accidental overdose, contact a poison control center immediately.

FOR CHRONIC ARTHRITIS

EXPECT A FAVORABLE SAFETY PROFILE



Color-enhanced 3-D CT image of normal stomach. Supplied by David W. Stoller, MD, of California Advanced Imaging.

As with other NSAIDs, the most frequent complaints are gastrointestinal, and rare hepatic and renal reactions have been reported.

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%.

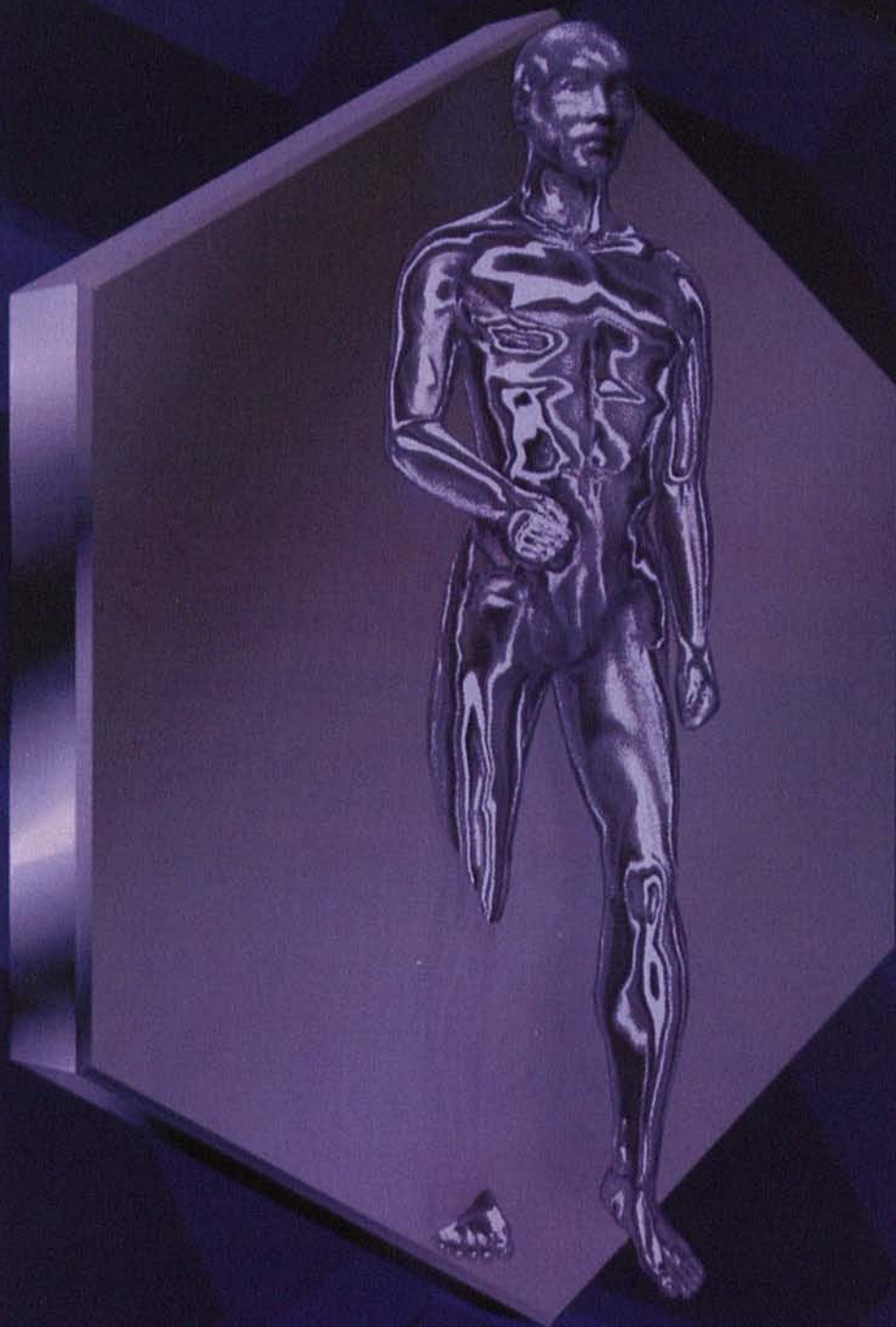
SYNTEX

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

 Rev. 39 September 1990

Lilly Research Laboratories
introduces a new oral antibiotic class

THE FIRST CARBACEPHEM



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FIRST IN A POTENT NEW CLASS

A new carbacephem.
Combination of benefits.

- Efficacy
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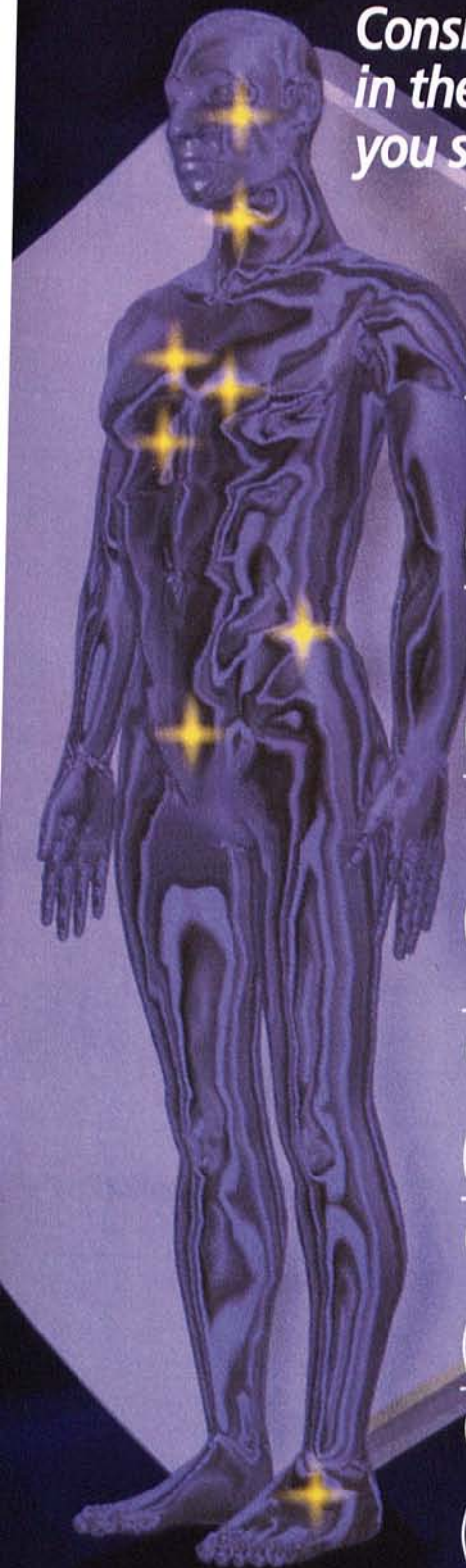
A broad range of clinical indications

Consistent clinical efficacy[1] at the end of treatment in the mild to moderate adult infections you see most often



95% (N=365) 62% cured, 33% improved

Secondary bacterial infection of acute bronchitis

Due to *S. pneumoniae*, *H. influenzae* (including β-lactamase-producing strains), and *M. catarrhalis* (including β-lactamase-producing strains).

93% (N=203) 54% cured, 39% improved

Acute bacterial exacerbations of chronic bronchitis

Due to *S. pneumoniae*, *H. influenzae* (including β-lactamase-producing strains), and *M. catarrhalis* (including β-lactamase-producing strains).

96% (N=83) 65% cured, 31% improved

Pneumonia

Due to *S. pneumoniae and H. influenzae* (non-β-lactamase-producing strains only).

97% (N=192) 65% cured, 32% improved

Acute maxillary sinusitis

Due to *S. pneumoniae*, *H. influenzae* (non-β-lactamase-producing strains only), and *M. catarrhalis* (including β-lactamase-producing strains). *Note:* In a patient population with significant numbers of β-lactamase-producing organisms, loracarbef's clinical cure and bacteriological eradication rates were somewhat less than those observed with a product containing a β-lactamase inhibitor. Lorabid's decreased potential for toxicity compared to products containing β-lactamase inhibitors along with the susceptibility patterns of the common microbes in a given geographic area should be taken into account when considering the use of an antimicrobial.

97% (N=180) 85% cured, 12% improved

Pharyngitis/tonsillitis

Due to *S. pyogenes*. *Note:* The usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever, is penicillin administered by the intramuscular route. Lorabid is generally effective in the eradication of *S. pyogenes* from the nasopharynx; however, data establishing the efficacy of Lorabid in the subsequent prevention of rheumatic fever are not available at present.

94% (N=68) 87% cured, 7% improved

Uncomplicated pyelonephritis

Due to *E. coli*.

90% (N=201) 84% cured, 6% improved

Uncomplicated urinary tract infections

Due to *E. coli* and *S. saprophyticus*. *Note:* In considering the use of Lorabid in the treatment of cystitis, Lorabid's lower bacterial eradication rates and lower potential for toxicity should be weighed against the increased eradication rates and increased potential for toxicity demonstrated by some other classes of approved agents.

93% (N=137) 67% cured, 26% improved

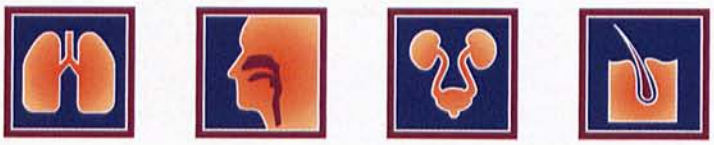
Uncomplicated skin and skin structure infections

Due to *S. aureus* (including penicillinase-producing strains) and *S. pyogenes*.

Coming soon in a suspension

See brief summary of prescribing information on adjacent page.

NEW CLASS
LORABID™
A STEP BEYOND...
LORACARBEF



Reference

1. Data on file, Lilly Research Laboratories.

Lorabid™
loracarbef
200-mg Pulvules®

Brief Summary. Consult the package insert for complete prescribing information.

Indications and Usage: Lorabid is a synthetic β-lactam antibiotic of the carbacephem class for oral administration. Lorabid is indicated in the following mild to moderate infections caused by susceptible strains of designated microorganisms.

Secondary Bacterial Infection of Acute Bronchitis caused by *Streptococcus pneumoniae, Haemophilus influenzae* (including β-lactamase-producing strains), or *Moraxella (Branhamella) catarrhalis* (including β-lactamase-producing strains).

Acute Bacterial Exacerbations of Chronic Bronchitis caused by *S. pneumoniae, H. influenzae* (including β-lactamase-producing strains), or *M. catarrhalis* (including β-lactamase-producing strains).

Pneumonia caused by *S. pneumoniae* or *H. influenzae* (non-β-lactamase-producing strains only).

Otitis Media* caused by *S. pneumoniae, H. influenzae* (including β-lactamase-producing strains), *M. catarrhalis* (including β-lactamase-producing strains), or *Streptococcus pyogenes*.

Acute Maxillary Sinusitis* caused by *S. pneumoniae, H. influenzae* (non-β-lactamase-producing strains only), or *M. catarrhalis* (including β-lactamase-producing strains).

*In a patient population with significant numbers of β-lactamase-producing organisms, loracarbef's clinical cure and bacteriological eradication rates were somewhat less than those observed with a product containing a β-lactamase inhibitor. Lorabid's decreased potential for toxicity compared to products containing β-lactamase inhibitors along with the susceptibility patterns of the common microbes in a given geographic area should be taken into account when considering the use of an antimicrobial (*see* Clinical Studies section).

Pharyngitis and Tonsillitis caused by *S. pyogenes*. (The usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever, is penicillin administered by the intramuscular route. Lorabid is generally effective in the eradication of *S. pyogenes* from the nasopharynx; however, data establishing the efficacy of Lorabid in the subsequent prevention of rheumatic fever are not available at present.)

Uncomplicated Skin and Skin Structure Infections caused by *Staphylococcus aureus* (including penicillinase-producing strains) or *S. pyogenes*. Abscesses should be surgically drained as clinically indicated.

Uncomplicated Urinary Tract Infections (cystitis) caused by *Escherichia coli* or *Staphylococcus saprophyticus**.

NOTE: In considering the use of Lorabid in the treatment of cystitis, Lorabid's lower bacterial eradication rates and lower potential for toxicity should be weighed against the increased eradication rates and increased potential for toxicity demonstrated by some other classes of approved agents (*see* Clinical Studies section).

Uncomplicated Pyelonephritis caused by *E. coli*.

*Although treatment of infections due to this organism in this organ system demonstrated a clinically acceptable overall outcome, efficacy was studied in fewer than 10 infections.

Contraindication: known allergy to loracarbef or cephalosporin-class antibiotics.

Warnings: Because cross-hypersensitivity can occur among β-lactams, Lorabid should be given cautiously to penicillin-sensitive patients and discontinued if an allergic reaction occurs.

Pseudomembranous colitis has been reported with nearly all antibacterial agents and should be considered in differential diagnosis of antibiotic-associated diarrhea.

Precautions: Lorabid may be administered to patients with impaired renal function. Total daily dosage should be reduced in patients with known or suspected renal impairment because of the possibility of high and/or prolonged plasma concentrations.

Loracarbef should be given cautiously to patients receiving diuretics concurrently.

Prolonged use may result in overgrowth of nonsusceptible organisms.

Loracarbef should be given cautiously to patients with a history of colitis.

Renal excretion of β-lactams is inhibited by probenecid and resulted in about an 80% increase in the AUC for loracarbef.

Safety and effectiveness have not been determined in pregnancy, lactation, and infants under 6 months of age. Caution should be exercised in prescribing Lorabid for these patients.

In geriatric patients who received the usual recommended adult doses in clinical studies, efficacy and safety were comparable to results in nongeriatric adult patients.

Adverse Reactions: Most adverse reactions in clinical trials were mild and transient. Only 1.5% of patients discontinued because of drug-related reactions, the most common of which were diarrhea, abdominal pain, and skin rashes.

All Patients

The incidence of the following adverse events was less than 1%, except as otherwise noted:

Gastrointestinal: Diarrhea, 4.1%; nausea, 1.9%; vomiting, 1.4%; abdominal pain, 1.4%; and anorexia.

Hypersensitivity: Skin rashes (1.2%), urticaria, pruritus, and erythema multiforme.

Central Nervous System: Headache (2.9%), somnolence, nervousness, insomnia, and dizziness.

Hemic and Lymphatic Systems: Transient thrombocytopenia, leukopenia, and eosinophilia.

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

Renal: Transient elevations in BUN and creatinine.

Cardiovascular System: Vasodilatation.

Genitourinary: Vaginitis (1.3%), vaginal moniliasis (1.1%).

Pediatric Patients

The incidences of several adverse events were significantly different in the pediatric population versus the adult population respectively as follows: Diarrhea (5.8% vs 3.6%); nausea (0.0% vs 2.5%); vomiting (3.3% vs 0.5%); anorexia (2.3% vs. 0.3%); headache (0.9% vs. 3.2%); somnolence (2.1% vs 0.4%); rhinitis (6.3% vs 1.6%); rash (2.9% vs 0.7%).

β-Lactam Antimicrobial Class Labeling:

Although not observed in Lorabid clinical trials, the following have been reported in patients treated with β-lactam antibiotics:

Adverse Reactions—Anaphylaxis, Stevens-Johnson syndrome, serum-sickness-like reactions, aplastic anemia, hemolytic anemia, hemorrhage, agranulocytosis, toxic epidermal necrolysis, renal dysfunction, toxic nephropathy, and hepatic dysfunction, including cholestasis, and seizures.

Altered Laboratory Tests—Increased prothrombin time, positive direct Coombs' test, elevated LDH, pancytopenia, and neutropenia.

Overdosage: Hemodialysis has been shown to be effective in hastening the elimination of loracarbef from plasma in patients with chronic renal failure.

Dosage and Administration: Lorabid is administered orally either at least 1 hour prior to eating or at least 2 hours after eating.

Population/Infection	Dosage (mg)	Duration (days)
Adults (≥13 years)		
Secondary Bacterial Infection of Acute Bronchitis	200-400 q 12h	7
Acute Bacterial Exacerbation of Chronic Bronchitis	400 q12h	7
Pneumonia	400 q12h	14
Pharyngitis/Tonsillitis	200 q12h	10
Sinusitis	400 q12h	10
(*See* Clinical Studies *and* Indications and Usage for further information.)		
Uncomplicated Skin and Skin Structure Infections	200 q12h	7
Uncomplicated cystitis	200 q24h	7
(*See* Clinical Studies *and* Indications and Usage for further information.)		
Uncomplicated pyelonephritis	400 q12h	14
Infants and Children (6 mos to 2 yrs)		
Acute Otitis Media*	30 mg/kg/day q12h (divided doses)	10
(*See* Clinical Studies *and* Indications and Usage for further information.)		
Pharyngitis/Tonsillitis	15 mg/kg/day q12h (divided doses)	10
Impetigo	15 mg/kg/day q12h (divided doses)	7

*Clinical studies of otitis media were conducted with the suspension formulation only. Therefore, the capsule should not be substituted for the suspension in the treatment of otitis media.

Clinical Studies:

Loracarbef (L) vs β-Lactamase Inhibitor (C) in Acute Otitis Media (US)

Efficacy: A study of acute otitis media performed in a population with a significant incidence of β-lactamase-producing organisms compared loracarbef with a β-lactamase inhibitor. Using very strict evaluability and microbiologic/clinical response criteria at the 10- to 16-day posttherapy follow-up, the following presumptive bacterial eradication/clinical cure outcomes (success rates) were obtained:

Pathogen	% Due to Pathogen (N = 204)	Success Rate
S. pneumoniae	42.6%	L equivalent to C
H. influenzae	30.4%	L 9% less than C
M. catarrhalis	20.6%	L 19% less than C
S. pyogenes	6.4%	L equivalent to C
Overall	100.0%	L 12% less than C

Safety: The incidences of the most common adverse events were clinically and statistically significantly higher in the control group versus the loracarbef group.

Event	Loracarbef	Control
Diarrhea	15%	26%
Rash*	8%	15%

*Primarily in the diaper area in young children.

Loracarbef (L) vs Amoxicillin (A) in Acute Otitis Media (Europe)

Efficacy: A study of acute otitis media performed in a population with a lower incidence of β-lactamase-producing organisms than that usually seen in US trials compared loracarbef to amoxicillin. Using very strict evaluability and microbiologic/clinical response criteria at the 10- to 16-day posttherapy follow-up, the following presumptive bacterial eradication/clinical cure outcomes (success rates) were obtained:

Pathogen	% Due to Pathogen (N = 291)	Success Rate
S. pneumoniae	51.5%	L equivalent to A
H. influenzae	29.2%	L 14% greater than A
M. catarrhalis	15.8%	L 31% greater than A
S. pyogenes	3.4%	L equivalent to A
Overall	100.0%	L equivalent to A

Loracarbef (L) vs Doxycycline (D) in Acute Maxillary Sinusitis (Europe)

Efficacy: A study of acute maxillary sinusitis performed in a population with a lower incidence of β-lactamase-producing organisms than that usually seen in US trials compared loracarbef with doxycycline. Using very strict evaluability (sinus-puncture) criteria and microbiologic/clinical response criteria at the 1- to 2-week posttherapy follow-up, the following presumptive bacterial eradication/clinical cure outcomes (success rates) were obtained:

Pathogen	% Due to Pathogen (N = 210)	Success Rate
S. pneumoniae	47.6%	L equivalent to D
H. influenzae	41.4%	L equivalent to D
M. catarrhalis	11.0%	L equivalent to D
Overall	100.0%	L equivalent to D

Loracarbef (L) vs Cefaclor (C) in Uncomplicated Cystitis Study (US)

Efficacy: A study of cystitis compared loracarbef with cefaclor. Using very strict evaluability criteria and microbiologic/clinical response criteria at the 5- to 9-day posttherapy follow-up, the following bacterial eradication rates were obtained:

Pathogen	% Due to Pathogen (N = 186)	Eradication Rate
E. coli	77.4%	L 4% greater than C (L = 80%)
Other major *Enterobacteriaceae*	12.5%	L equivalent to C (L = 61%)
S. saprophyticus	3.8%	L equivalent to C

Loracarbef (L) vs Quinolone (Q) in Uncomplicated Cystitis (Europe)

Efficacy: A study of cystitis compared loracarbef with an oral quinolone. Using very strict evaluability criteria and microbiologic/clinical response criteria at the 5- to 9-day posttherapy follow-up, the following bacterial eradication rates were obtained:

Pathogen	% Due to Pathogen (N = 189)	Eradication Rate
E. coli	82.0%	L 7% less than Q (L = 81%)
Other major *Enterobacteriaceae*	10.1%	L 32% less than Q (L = 50%)

PV 2731 AMP [032592]

Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285.

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Unique dual mechanism of action

Controls hypertension through a combination of mild diuresis and vasodilatation[1,2]

Gradually reduces both systolic and diastolic blood pressures[3,4]

Well-tolerated hypertension control

Low patient dropout rate due to favorable side-effect profile and convenient once-daily dosing[5]

Does not adversely affect lipids[6-9]

kindhearted ONCE A DAY
LOZOL®
INDAPAMIDE 2.5mg TABLETS

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. Campbell DB: The possible mode of action of indapamide: A review. *Curr Med Res Opin* 1983;8(Suppl 3):9-24. 2. Wilson PR, Kem DC: Indapamide. In: Messerli FH, ed. *Cardiovascular Drug Therapy*. Philadelphia: W.B. Saunders Co. 1990;348-356. 3. Mimran A, Zambrowski JJ, Coppolani T: The antihypertensive action of indapamide: Results of a French multicentre study of 2,184 ambulant patients. *Postgrad Med J* 1981;57(Suppl 2):60-63. 4. Data on file, Rhône-Poulenc Rorer Pharmaceuticals Inc. 5. Abbou C-B: The efficacy and tolerance of indapamide in essential hypertension: A multi-centre study in 981 patients. *Curr Med Res Opin* 1985;9(7):494-499. 6. Beling S, Vukovich RA, Neiss ES, et al: Long-term experience with indapamide. *Am Heart J* 1983;106(1, Part 2):258-262. 7. 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.
8. 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. 9. Horgan JH, O'Donovan A, Teo KK: Echocardiographic evaluation of left ventricular function in patients showing an antihypertensive and biochemical response to indapamide. *Postgrad Med J* 1981;57(Suppl 2):64-67.

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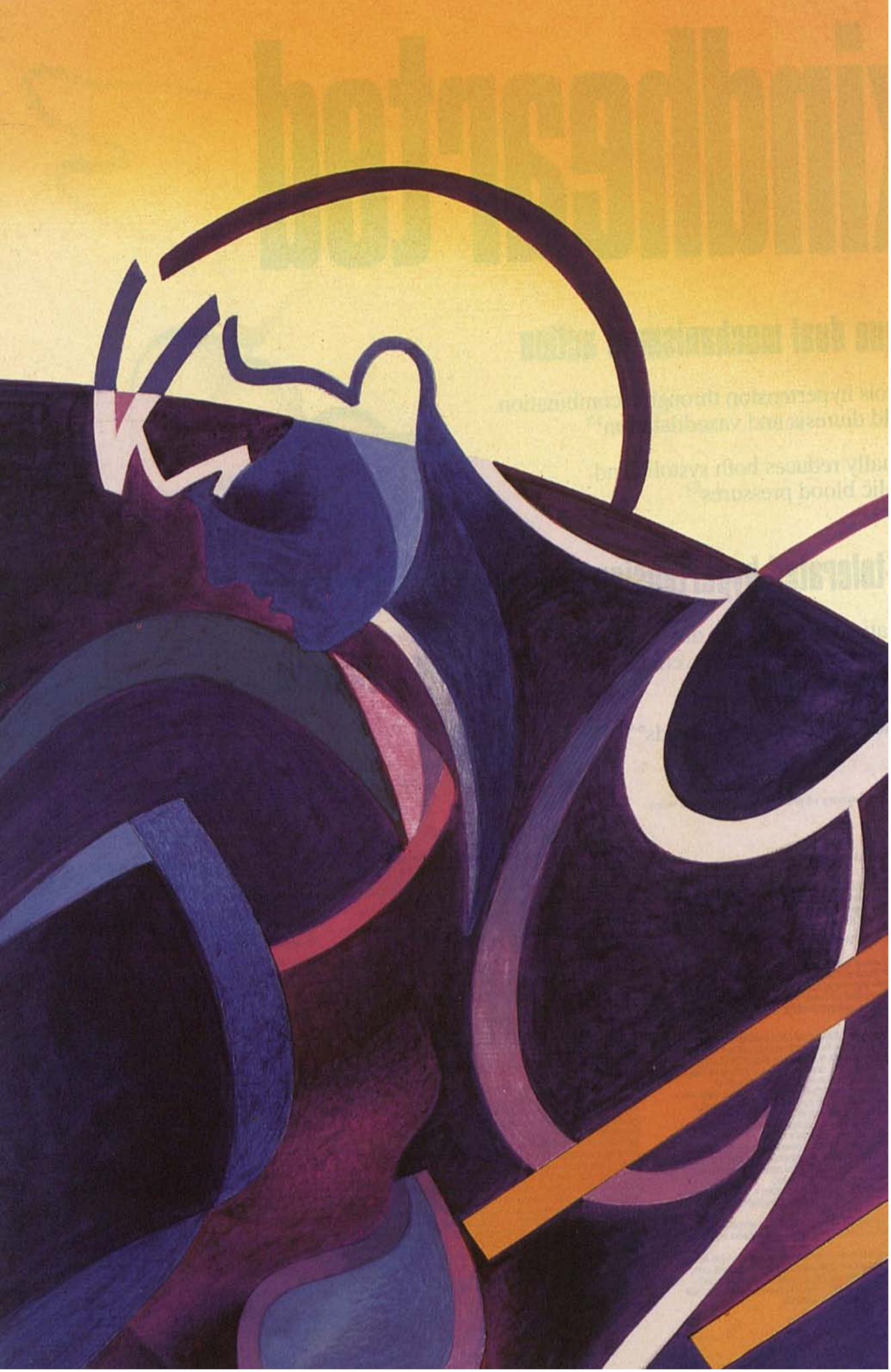


Announcing the first of a new NSAID class

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 (14%), dyspepsia (13%) and abdominal pain (12%)

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

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.

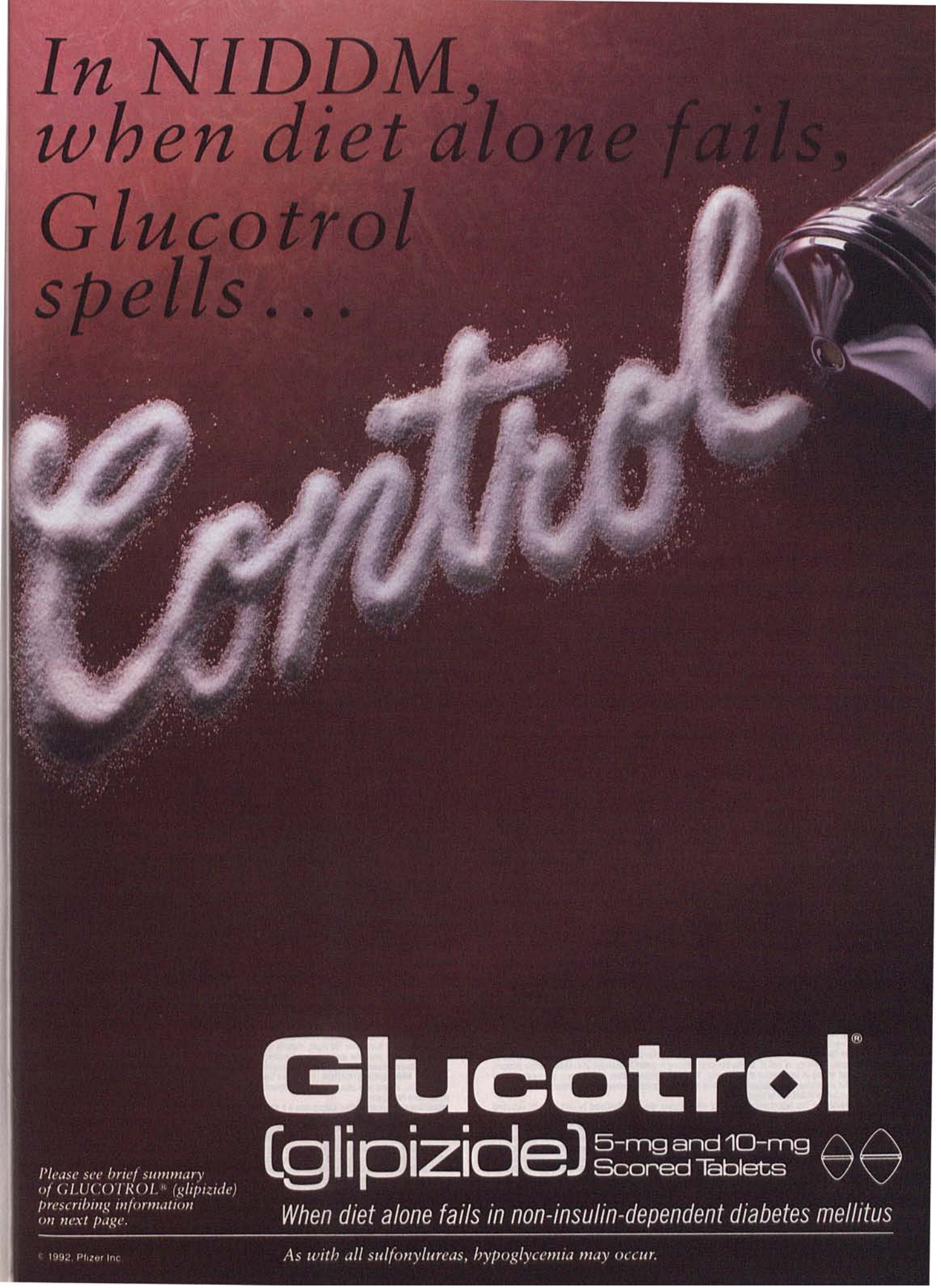
DOSAGE AND ADMINISTRATION: Recommended starting dose: 1000 mg taken as a single dose with or without food. Some patients may obtain more symptomatic relief from 1500 mg to 2000 mg daily. Dosages over 2000 mg daily have not been studied. Use the lowest effective dose for chronic treatment.

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


In NIDDM, when diet alone fails, Glucotrol spells...
control
Glucotrol®
(glipizide) 5-mg and 10-mg Scored Tablets
When diet alone fails in non-insulin-dependent diabetes mellitus
As with all sulfonylureas, hypoglycemia may occur.
Please see brief summary of GLUCOTROL® (glipizide) prescribing information on next page.
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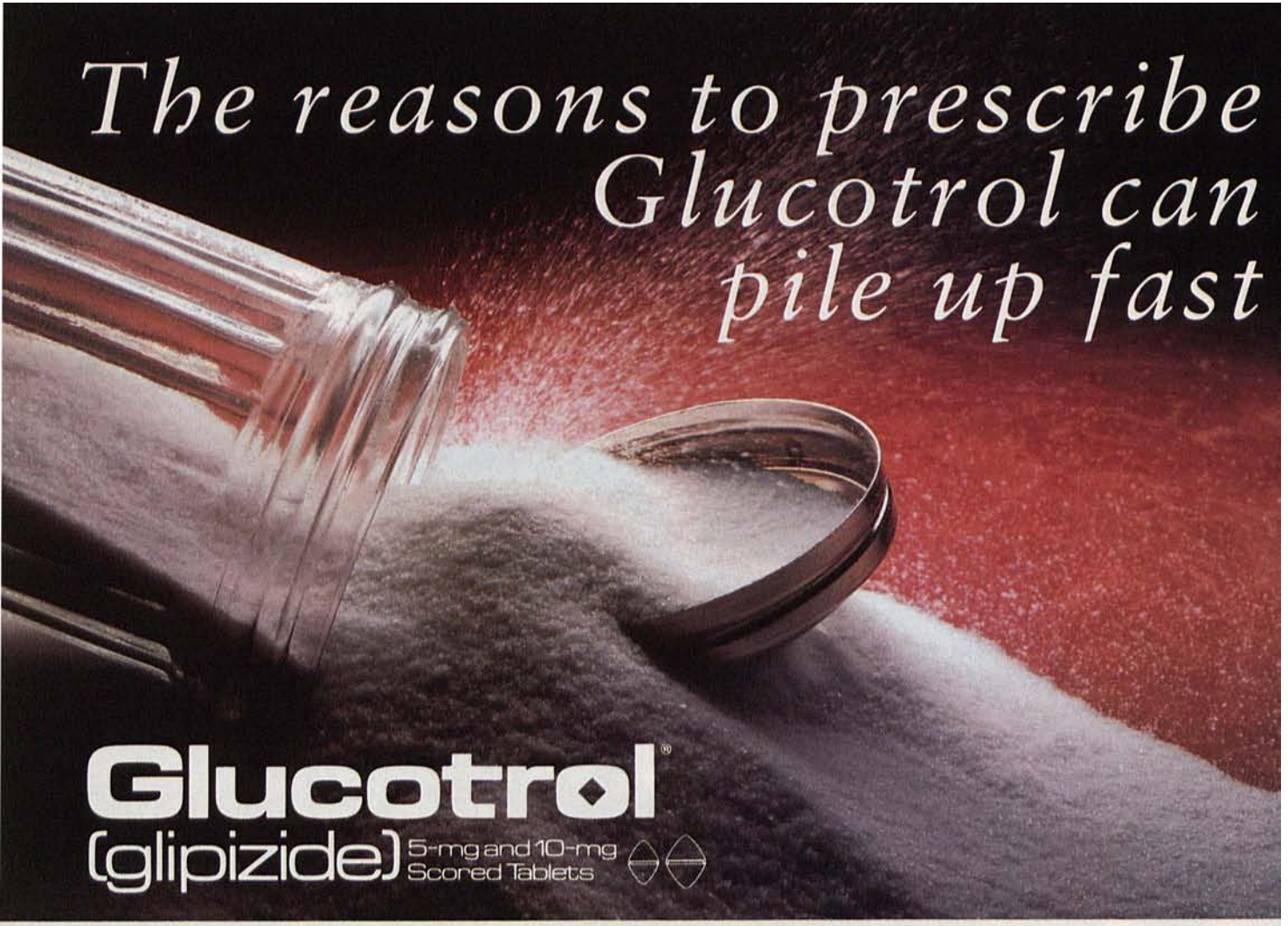


Brief Summary of Prescribing Information

INDICATIONS AND USAGE: GLUCOTROL is indicated as an adjunct to diet for the control of hyperglycemia in patients with non-insulin-dependent diabetes mellitus (NIDDM; type II), after an adequate trial of dietary therapy has proved unsatisfactory.

CONTRAINDICATIONS: GLUCOTROL is contraindicated in patients with known hypersensitivity to the drug or with diabetic ketoacidosis, with or without coma, which should be treated with insulin.

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY: The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (*Diabetes*, 19, supp. 2:747-830, 1970). UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2½ times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of GLUCOTROL and of alternative modes of therapy. Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

PRECAUTIONS: Renal and Hepatic Disease: The metabolism and excretion of GLUCOTROL may be slowed in patients with impaired renal and/or hepatic function. Hypoglycemia may be prolonged in such patients should it occur.

Hypoglycemia: All sulfonylureas are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemia. Renal or hepatic insufficiency may increase the risk of hypoglycemic reactions. Elderly, debilitated or malnourished patients and those with adrenal or pituitary insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly or people taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

Loss of Control of Blood Glucose: A loss of control may occur in diabetic patients exposed to stress such as fever, trauma, infection, or surgery. It may then be necessary to discontinue GLUCOTROL and administer insulin.

Laboratory Tests: Blood and urine glucose should be monitored periodically. Measurement of glycosylated hemoglobin may be useful.

Information for Patients: Patients should be informed of the potential risks and advantages of GLUCOTROL, of alternative modes of therapy, as well as the importance of adhering to dietary instructions, of a regular exercise program, and of regular testing of urine and/or blood glucose. The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. Primary and secondary failure should also be explained.

Drug Interactions: The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta-adrenergic blocking agents. *In vitro* studies indicate that GLUCOTROL binds differently than tolbutamide and does not interact with salicylate or dicumarol. However, caution must be exercised in extrapolating these findings to the clinical situation. Certain drugs tend to produce hyperglycemia and may lead to loss of control, including the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: A 20-month study in rats and an 18-month study in mice at doses up to 75 times the maximum human dose revealed no evidence of drug-related carcinogenicity. Bacterial and *in vivo* mutagenicity tests were uniformly negative. Studies in rats of both sexes at doses up to 75 times the human dose showed no effects on fertility.

Pregnancy: Pregnancy Category C: GLUCOTROL (glipizide) was found to be mildly fetotoxic in rat reproductive studies at all dose levels (5-50 mg/kg). This fetotoxicity has been similarly noted with other sulfonylureas, such as tolbutamide and tolazamide. The effect is perinatal and believed to be directly related to the pharmacologic (hypoglycemic) action of GLUCOTROL. In studies in rats and rabbits no teratogenic effects were found. There are no adequate and well-controlled studies in pregnant women. GLUCOTROL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nonteratogenic Effects: Prolonged severe hypoglycemia has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. GLUCOTROL should be discontinued at least one month before the expected delivery date.

Nursing Mothers: Since some sulfonylurea drugs are known to be excreted in human milk, Insulin therapy should be considered if nursing is to be continued.

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

ADVERSE REACTIONS: In controlled studies, the frequency of serious adverse reactions reported was very low. Of 702 patients, 11.8% reported adverse reactions and in only 1.5% was GLUCOTROL discontinued.

Hypoglycemia: See PRECAUTIONS and OVERDOSAGE sections.

Gastrointestinal: Gastrointestinal disturbances, the most common, were reported with the following approximate incidence: nausea and diarrhea, one in 70; constipation and gastralgia, one in 100. They appear to be dose-related and may disappear on division or reduction of dosage. Cholestatic jaundice may occur rarely with sulfonylureas: GLUCOTROL should be discontinued if this occurs.

Dermatologic: Allergic skin reactions including erythema, morbilliform or maculopapular eruptions, urticaria, pruritus, and eczema have been reported in about one in 70 patients. These may be transient and may disappear despite continued use of GLUCOTROL; if skin reactions persist, the drug should be discontinued. Porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas.

Hematologic: Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas.

Metabolic: Hepatic porphyria and disulfiram-like alcohol reactions have been reported with sulfonylureas. Clinical experience to date has shown that GLUCOTROL has an extremely low incidence of disulfiram-like reactions.

Endocrine Reactions: Cases of hyponatremia and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion have been reported with this and other sulfonylureas.

Miscellaneous: Dizziness, drowsiness, and headache have each been reported in about one in fifty patients treated with GLUCOTROL. They are usually transient and seldom require discontinuance of therapy.

OVERDOSAGE: Overdosage of sulfonylureas including GLUCOTROL can produce hypoglycemia. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours since hypoglycemia may recur after apparent clinical recovery. Clearance of GLUCOTROL from plasma would be prolonged in persons with liver disease. Because of the extensive protein binding of GLUCOTROL, dialysis is unlikely to be of benefit.

DOSAGE AND ADMINISTRATION: There is no fixed dosage regimen for the management of diabetes mellitus with GLUCOTROL; in general, it should be given approximately 30 minutes before a meal to achieve the greatest reduction in postprandial hyperglycemia.

Initial Dose: The recommended starting dose is 5 mg before breakfast. Geriatric patients or those with liver disease may be started on 2.5 mg. Dosage adjustments should ordinarily be in increments of 2.5–5 mg, as determined by blood glucose response. At least several days should elapse between titration steps.

Maximum Dose: The maximum recommemded total daily dose is 40 mg.

Maintenance: Some patients may be effectively controlled on a once-a-day regimen, while others show better response with divided dosing. Total daily doses above 15 mg should ordinarily be divided.

HOW SUPPLIED: GLUCOTROL tablets are white, dye-free, scored, diamond-shaped, and imprinted as follows:

5 mg—Pfizer 411; 10 mg—Pfizer 412.

5 mg Bottles: 100's (NDC 0049-4110-66); 500's (NDC 0049-4110-73); Unit Dose 100's (NDC 0049-4110-41)

10 mg Bottles: 100's (NDC 0049-4120-66); 500's (NDC 0049-4120-73); Unit Dose 100's (NDC 0049-4120-41)

CAUTION: Federal law prohibits dispensing without prescription.

More detailed professional information available on request.

Pfizer Roerig

Revised August 1990

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®

(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.

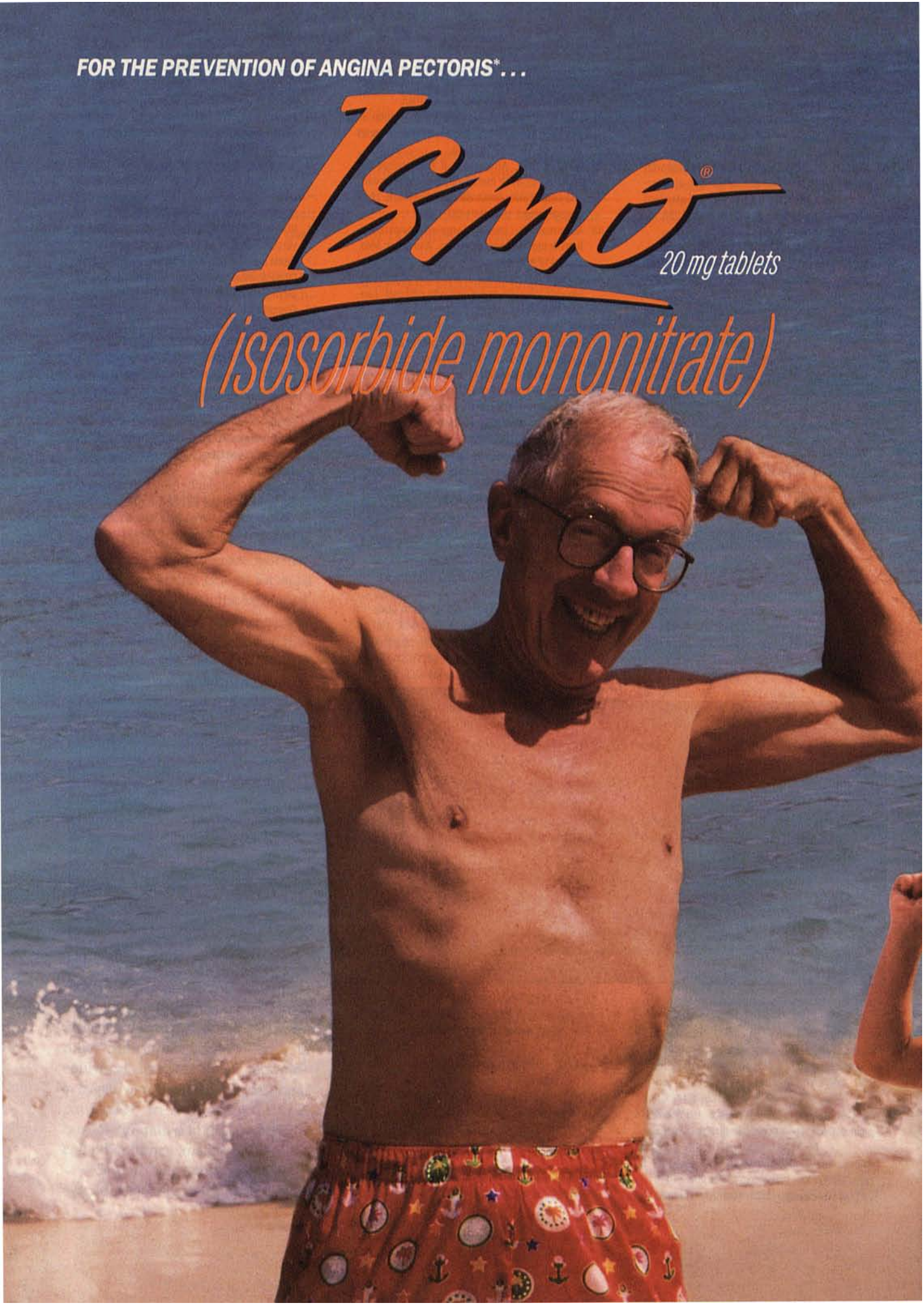
INDICATIONS AND USAGE: For the relief of moderate to moderately severe pain. **CONTRAINDICATIONS:** Hypersensitivity to acetaminophen or hydrocodone. **WARNINGS: Respiratory Depression:** At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression. **Head Injury 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®


FOR THE PREVENTION OF ANGINA PECTORIS*...
Ismo®
20 mg tablets
(isosorbide mononitrate)

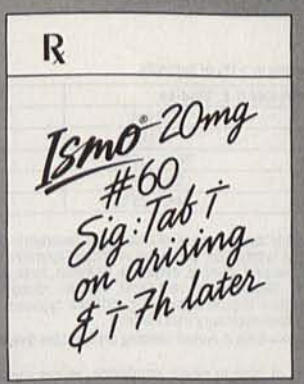
ACTIVITY YOU CAN COUNT ON

- **Demonstrated efficacy for at least 12 hours after the first dose (ie, 5 hours after the second dose)**
- **Avoids tolerance and rebound when dosed as recommended†**

The most common side effect, headache, may be resolved with mild analgesics. As with other long-acting nitrates, Ismo is not recommended in patients with acute myocardial infarction or congestive heart failure.

*Ismo is not recommended for use in aborting acute anginal episodes.

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



Ismo® 20 mg tablets

(isosorbide mononitrate)

Count on it.

Please see brief summary of prescribing information on adjacent page.

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.

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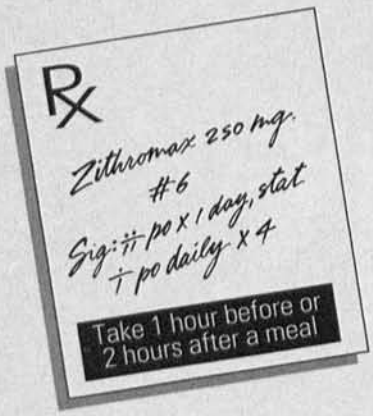

- **For respiratory infections such as acute bacterial exacerbations of COPD (chronic bronchitis) and uncomplicated skin infections:** 500-mg single dose on day 1; 250 mg once daily on days 2 through 5. Total dose is 1.5 g.
- **Zithromax should be given either 1 hour before or 2 hours after a meal.**
- **A favorable safety profile** with a low (0.7%; n=4949) discontinuation rate due to side effects. In multidose trials, the most common side effects were diarrhea/loose stools (5%), nausea (3%), and abdominal pain (3%).[1]

References: 1. Data on file. Pfizer Inc, New York, NY. **2.** Baldwin DR, Wise R, Andrews JM, Ashby JP, Honeybourne D. Azithromycin concentrations at the sites of pulmonary infection. *Eur Respir J.* 1990;3:886-890. **3.** Girard AE, Cimochowski CR, Faiella JA. Correlation of increased azithromycin levels with phagocyte infiltration into sites of infection. [Abstract 762]. Thirtieth Interscience Conference on Antimicrobial Agents and Chemotherapy; 1990. **4.** Retsema J, Bergeron J, Girard D, Wilsen W, Schelkly W, Girard A. Preferential concentration of azithromycin in infected mouse thighs as compared to contralateral non-infected thighs. [Abstract A-63]. 91st General Meeting of the American Society for Microbiology; 1991. **5.** Gladue RP, Bright GM, Isaacson RE, Newborg MF. In vitro and in vivo uptake of azithromycin (CP-62,993) by phagocytic cells: possible mechanism of delivery and release at sites of infection. *Antimicrob Agents Chemother.* 1989;33:277-282.

ZITHROMAX® (azithromycin) CAPSULES
BRIEF SUMMARY
INDICATIONS AND USAGE

ZITHROMAX® (azithromycin) is indicated for the treatment of individuals 16 years of age and older with mild to moderate infections (pneumonia: see WARNINGS) caused by susceptible strains of the designated microorganisms in the specific conditions listed below:

Lower Respiratory Tract
Acute bacterial exacerbations of chronic obstructive pulmonary disease due to *Haemophilus influenzae, Moraxella catarrhalis,* or *Streptococcus pneumoniae.*

Community-acquired pneumonia of mild severity due to *Streptococcus pneumoniae* or *Haemophilus influenzae* in patients appropriate for outpatient oral therapy.

Note: Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for outpatient oral therapy because of moderate to severe illness or risk factors such as any of the following:
patients with nosocomially acquired infections,
patients with known or suspected bacteremia,
patients requiring hospitalization,
elderly or debilitated patients, or
patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

Upper Respiratory Tract
Streptococcal pharyngitis/tonsillitis—As an alternative to first line therapy of acute pharyngitis/tonsillitis due to *Streptococcus pyogenes* occurring in individuals who cannot use first line therapy.

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

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

Sexually Transmitted Diseases
Non-gonococcal urethritis and cervicitis due to *Chlamydia trachomatis.*

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

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

CONTRAINDICATIONS

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

WARNINGS

Rare serious allergic reactions, including angioedema and anaphylaxis, have been reported in patients on azithromycin therapy. (See **CONTRAINDICATIONS.**) Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms **recurred soon thereafter in some patients without further azithromycin exposure.** These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long tissue half-life of azithromycin and subsequent prolonged exposure to antigen is unknown at present.

If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

In the treatment of pneumonia, azithromycin has only been shown to be safe and effective in the treatment of community-acquired pneumonia of mild severity due to *Streptococcus pneumoniae* or *Haemophilus influenzae* in patients appropriate for outpatient oral therapy. Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for outpatient oral therapy because of moderate to severe illness or risk factors such as any of the following:

patients with nosocomially acquired infections,
patients with known or suspected bacteremia,
patients requiring hospitalization,
elderly or debilitated patients, or
patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

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

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

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

PRECAUTIONS

General: Because azithromycin is principally eliminated via the liver, caution should be exercised when azithromycin is administered to patients with impaired hepatic function. There are no data regarding azithromycin usage in patients with renal impairment; thus caution should be exercised when prescribing azithromycin in these patients.

The following adverse event has not been reported in clinical trials with azithromycin, an azalide. However, it has been reported with macrolide products: ventricular arrhythmias, including ventricular tachycardia and *torsades de pointes,* in individuals with prolonged QT intervals.

Information for Patients: Patients should be cautioned to take this medication at least one hour prior to a meal or at least two hours after a meal. This medication should not be taken with food.

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

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

Drug Interactions: Aluminum- and magnesium-containing antacids reduce the peak serum levels (rate) but not the AUC (extent) of azithromycin absorption.

Administration of cimetidine (800 mg) two hours prior to azithromycin had no effect on azithromycin absorption.

Azithromycin did not affect the plasma levels or pharmacokinetics of theophylline administered as a single intravenous dose. The effect of azithromycin on the plasma levels or pharmacokinetics of theophylline administered in multiple doses resulting in therapeutic steady state levels of theophylline is not known. However, concurrent use of macrolides and theophylline has been associated with increases in the serum concentrations of theophylline. Therefore, until further data are available, prudent medical practice dictates careful monitoring of plasma theophylline levels in patients receiving azithromycin and theophylline concomitantly.

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

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

Digoxin—elevated digoxin levels.
Ergotamine or dihydroergotamine—acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.
Triazolam—decrease the clearance of triazolam and thus may increase the pharmacologic effect of triazolam.
Drugs metabolized by the cytochrome P_{450} system—elevations of serum carbamazepine, cyclosporine, hexobarbital, and phenytoin levels.

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

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

Pregnancy: Teratogenic Effects. Pregnancy Category B: Reproduction studies have been performed in rats and mice at doses up to moderately maternally toxic dose levels (*i.e.,* 200 mg/kg/day). These doses, based on a mg/m² basis, are estimated to be 4 and 2 times, respectively, the human daily dose of 500 mg. No evidence of impaired fertility or harm to the fetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed.

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

Pediatric Use: Safety and effectiveness in children or adolescents under 16 years of age have not been established.

Geriatric Use: Pharmacokinetic parameters in older volunteers (65-85 years old) were similar to those in younger volunteers (18-40 years old) for the 5-day therapeutic regimen. Dosage adjustment does not appear to be necessary for older patients with normal renal and hepatic function receiving treatment with this dosage regimen.

ADVERSE REACTIONS

In clinical trials most of the reported side effects were mild to moderate in severity and were reversible upon discontinuation of the drug. Approximately 0.7% of the patients from the multiple dose clinical trials discontinued ZITHROMAX® (azithromycin) therapy because of treatment-related side effects. Most of the side effects leading to discontinuation were related to the gastrointestinal tract, e.g., nausea, vomiting, diarrhea, or abdominal pain. Rare, but potentially serious side effects, were angioedema and cholestatic jaundice.

Clinical:
Multiple-dose regimen: Overall, the most common side effects in patients receiving the multiple-dose regimen of ZITHROMAX® were related to the gastrointestinal system with diarrhea/loose stools (5%), nausea (3%), and abdominal pain (3%) being the most frequently reported.

No other side effects occurred in patients on the multiple-dose regimen of ZITHROMAX® with a frequency greater than 1%. Side effects that occurred with a frequency of 1% or less included the following:

Cardiovascular: Palpitations, chest pain.
Gastrointestinal: Dyspepsia, flatulence, vomiting, melena, and cholestatic jaundice.
Genitourinary: Monilia, vaginitis, and nephritis.
Nervous System: Dizziness, headache, vertigo, and somnolence.
General: Fatigue.
Allergic: Rash, photosensitivity, and angioedema.

Single 1-gram dose regimen: Overall, the most common side effects in patients receiving a single-dose regimen of 1 gram of ZITHROMAX® were related to the gastrointestinal system and were more frequently reported than in patients receiving the multiple-dose regimen.

Side effects that occurred in patients on the single one-gram dosing regimen of ZITHROMAX® with a frequency of 1% or greater included diarrhea/loose stools (7%), nausea (5%), vomiting (2%), and vaginitis (2%).

Laboratory Abnormalities: Significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows:

With an incidence of 1-2%: elevated serum creatine phosphokinase, potassium, ALT (SGPT), GGT, and AST (SGOT).

With an incidence of less than 1%: leukopenia, neutropenia, decreased platelet count, elevated serum alkaline phosphatase, bilirubin, BUN, creatinine, blood glucose, LDH, and phosphate.

When follow-up was provided, changes in laboratory tests appeared to be reversible.

In multiple-dose clinical trials involving more than 3000 patients, 3 patients discontinued therapy because of treatment-related liver enzyme abnormalities and 1 because of a renal function abnormality.

DOSAGE AND ADMINISTRATION (See INDICATIONS AND USAGE)

ZITHROMAX® (azithromycin) should be given at least 1 hour before or 2 hours after a meal.

The recommended dose of ZITHROMAX® for the treatment of individuals 16 years of age and older with mild to moderate acute bacterial exacerbations of chronic obstructive pulmonary disease, pneumonia, pharyngitis/tonsillitis (as second-line therapy), and uncomplicated skin and skin structure infections due to the indicated organisms is: 500 mg as a single dose on the first day followed by 250 mg once daily on days 2 through 5 for a total dose of 1.5 grams of ZITHROMAX®.

The recommended dose of ZITHROMAX® for the treatment of non-gonococcal urethritis and cervicitis due to *C. trachomatis* is a single 1 gram (1000 mg) dose of ZITHROMAX®.

More detailed professional information available on request.

Revised October 1992

Pfizer

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INDEX TO ADVERTISERS

While every precaution is taken to ensure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.