Today's hypertensives with new concerns...

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

THE CARDURA GENERATION

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

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

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

ONCE-A-DAY

CARDURA®

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

HYPERTENSION CONTROL FOR A NEW GENERATION.

Please see brief summary of prescribing information on next page.

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

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

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

WARNINGS

Syncope and "First-dose" Effect:

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

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

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

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

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

PRECAUTIONS

General

1. Orthostatic Hypotension:

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

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

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

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

2. Impaired liver function:

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

3. Leukopenia/Neutropenia:

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

Information for Patients:

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

Drug Interactions:

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

Drug/Laboratory test interactions:

None known.

Cardiac Toxicity in Animals:

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

Carcinogenesis, Mutagenesis and Impairment of Fertility:

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

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

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

Pregnancy

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

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

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

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

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

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

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

TABLE 1
ADVERSE REACTIONS DURING PLACEBO CONTROLLED STUDIES

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

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

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

OVERDOSAGE

No data are available in regard to overdosage in humans.

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

DOSAGE AND ADMINISTRATION

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

HOW SUPPLIED

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

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

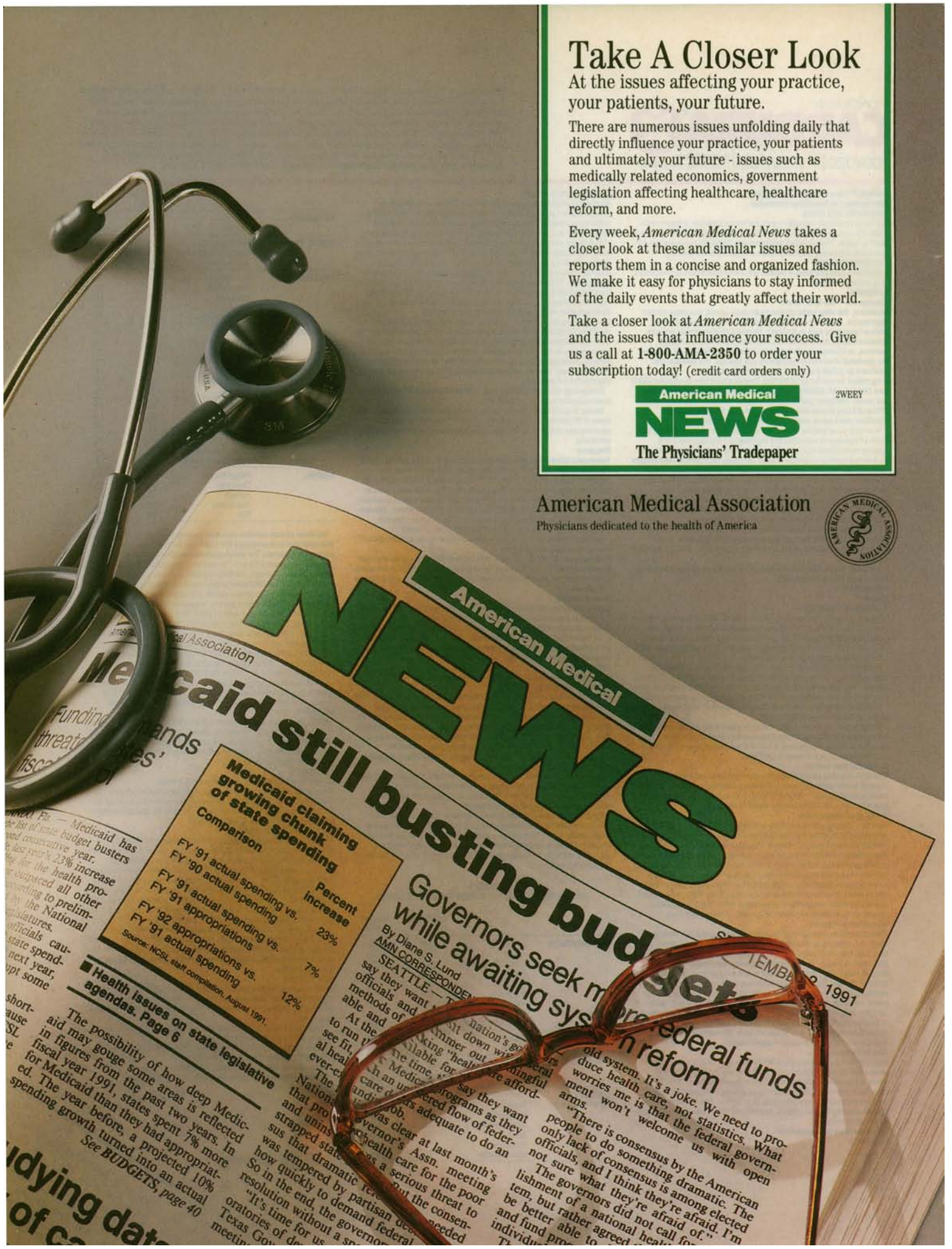
Bottles of 100: 1 mg (NDC 0049-2750-66), 2 mg (NDC 0049-2760-66), 4 mg (NDC 0049-2770-66), 8 mg (NDC 0049-2780-66)

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

CAUTION: Federal law prohibits dispensing without prescription.

65-4538-00-0 Issued Nov 1990

Pfizer Roerig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Governors seek more federal funds while awaiting system reform
Medicaid claiming growing chunk of state spending
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FY '91 actual spending vs. FY '91 appropriations 7%
FY '92 appropriations vs. FY '91 actual spending 12%
Source: NCSL staff compilation, August 1991.
Health issues on state legislative agendas. Page 6
By Diane S. Lund
AMN CORRESPONDENT
SEPTEMBER 9, 1991

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

VERELAN

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

Incidence of side effects commonly associated with calcium channel blockers

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

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

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

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

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

ONCE-A-DAY

VERELAN®

Verapamil HCl 120 mg 180 mg 240 mg

PELLET-FILLED CAPSULES

ARCHIVES OF FAMILY MEDICINE

VOL 2 NO. 7, JULY 1993

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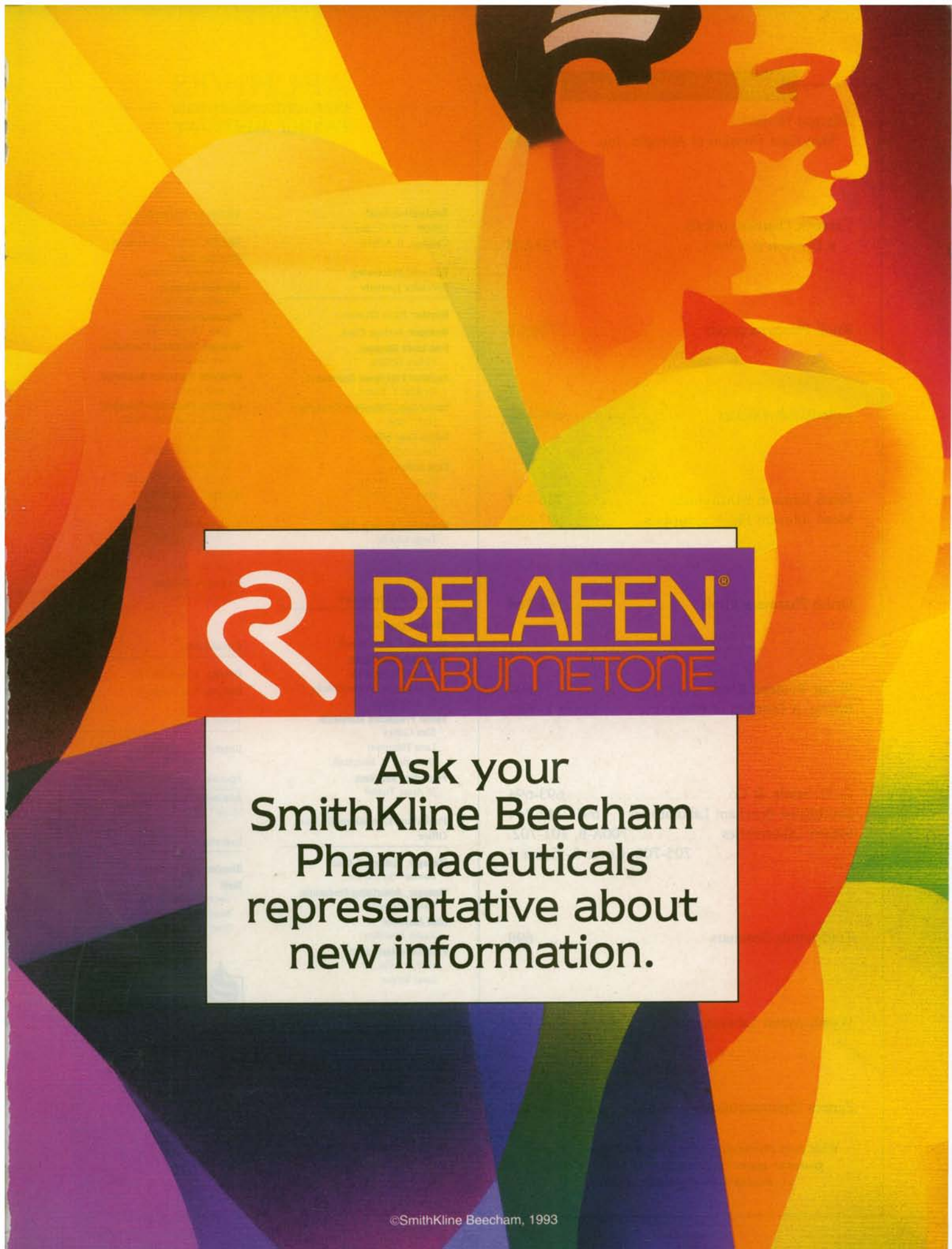
Physicians dedicated to the health of America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In osteoarthritis and adult rheumatoid arthritis

Get

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

DAYPRO™

(oxaprozin) 600-mg caplets

All you want in an NSAID†

Efficacy **Tolerability** **Once-a-day dosing**

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

† Nonsteroidal anti-inflammatory drug.

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

Please see brief summary of prescribing information on following page.

SEARLE

Get New **DAYPRO**™ (oxaprozin) 600-mg caplets

All you want in an NSAID

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

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

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

BRIEF SUMMARY

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

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

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

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

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

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

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

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

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

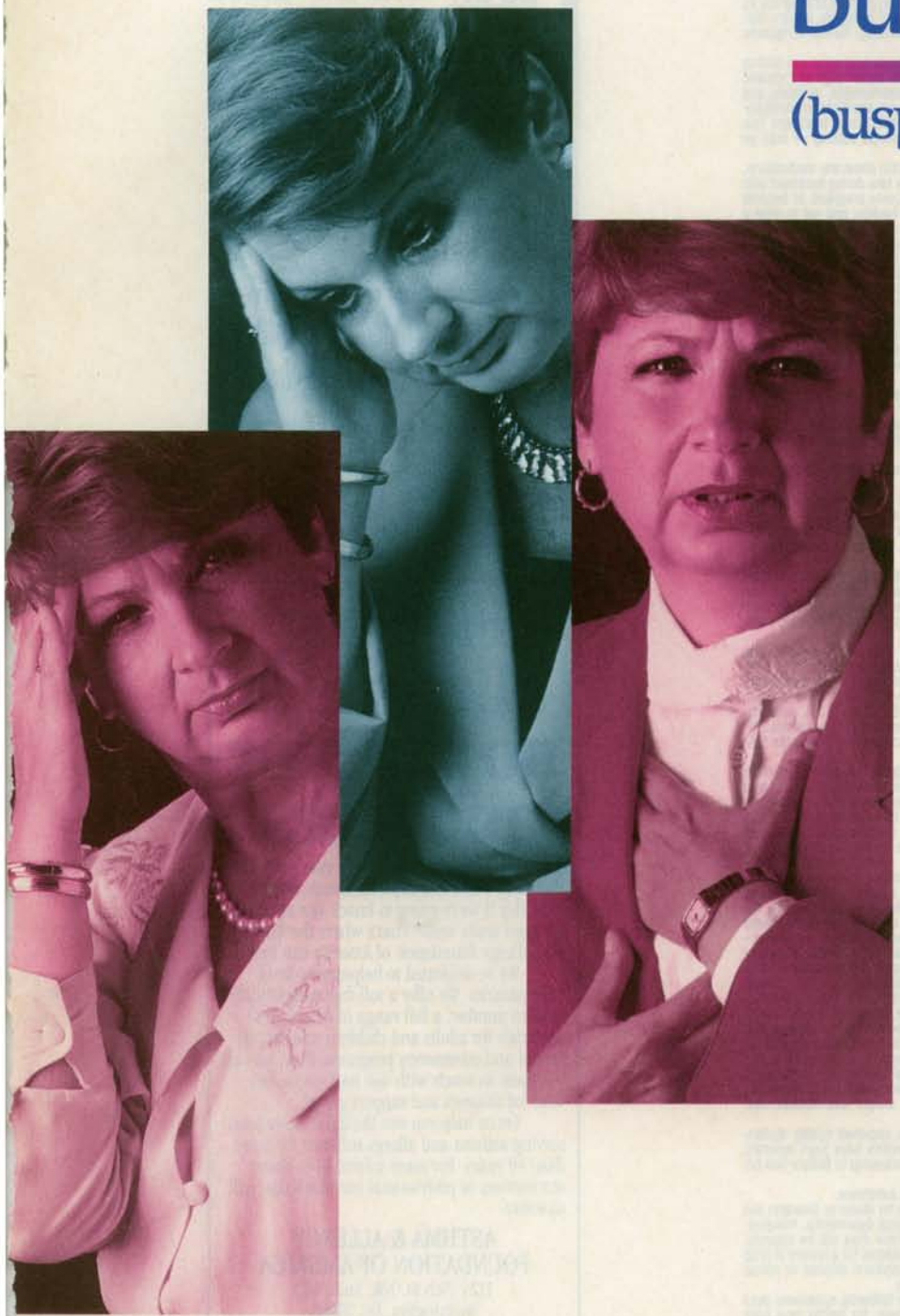
2/2/93 • P93DA7916V

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

SEARLE

Box 5110
Chicago, IL 60680-5110

BECAUSE APPROXIMATELY 60% OF PATIENTS WITH PERSISTENT ANXIETY MAY EXHIBIT DEPRESSIVE SYMPTOMS...[1]



BuSpar® 10mg

(buspirone HCl)

Now indicated for the relief of persistent anxiety with coexisting depressive symptoms.*

- Anxiolytic efficacy demonstrated in anxious patients with or without coexisting depressive symptoms.[2]
- Relief of anxiety symptoms begins within 1 week, progresses steadily through the fourth week of therapy.[3]
- Nonaddictive, no more sedation (10%) than seen with placebo (9%).[4,5]
- The more commonly observed untoward events include dizziness (12%), nausea (8%), headache (6%), and nervousness (5%).

Progressive Relief of Persistent Anxiety.

*BuSpar is not indicated for the relief of primary depressive disorder.

Please see references and brief summary on adjacent page.

BuSpar® (buspirone HCl)

References: 1. Data on file, Bristol-Myers Squibb Company. **2.** Cohn JB, Bowden CL, Fisher JG, Rodos JJ. Double-blind comparison of buspirone and clorazepate in anxious outpatients with or without depressive symptoms. *Psychopathology.* 1992;25:10-21. **3.** Feighner JP, Cohn JB. Analysis of individual symptoms in generalized anxiety—a pooled, multistudy, double-blind evaluation of buspirone. *Neuropsychopiology.* 1989;21:124-130. **4.** Lader M. Assessing the potential for buspirone dependence or abuse and effects of its withdrawal. *Am J Med.* 1987;82(suppl 5A):20-26. **5.** Newton RE, Marunycz JD, Alderdice MT, Napolitello MJ. Review of the side-effect profile of buspirone. *Am J Med.* 1986;80(suppl 3B):17-21.

Contraindications: Hypersensitivity to buspirone hydrochloride.

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: ***General*** – *Interference with cognitive and motor performance:* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).

Information for Patients – Patients should be instructed to inform their physician about any medications, prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Drug Interactions – Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations of SGPT (ALT) in a few patients. Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol concentrations in normal volunteers. The clinical significance is not clear. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin. However, there was one report of prolonged prothrombin time when buspirone was given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid.

Carcinogenesis, Mutagenesis, Impairment of Fertility – No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

Pregnancy: Teratogenic Effects – Pregnancy Category B: Should be used during pregnancy only if clearly needed.

Nursing Mothers – Administration to nursing women should be avoided if clinically possible.

Pediatric Use – The safety and effectiveness have not been determined in individuals below 18 years of age.

Use in the Elderly – No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

Use in Patients with Impaired Hepatic or Renal Function – Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): ***Commonly Observed*** – The more commonly observed untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

Associated with Discontinuation of Treatment – The more common events causing discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials – Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular:* Tachycardia/palpitations 1%. *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT:* Blurred vision 2%. *Gastrointestinal:* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal:* Musculoskeletal aches/pains 1%. *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin:* Skin rash 1%. *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Premarketing Evaluation – The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. *Cardiovascular* – frequent: non-specific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System* – frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT* – frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine* – rare: galactorrhea, thyroid abnormality. *Gastrointestinal* – infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary* – infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal* – infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological* – infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory* – infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function* – infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin* – infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory* – infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous* – infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

Postintroduction Clinical Experience – Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported. Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined.

Drug Abuse and Dependence: ***Controlled Substance Class*** – Not a controlled substance.

Physical and Psychological Dependence – Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: ***Signs and Symptoms*** – At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

Recommended Overdosage Treatment – General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.

U.S. Patent Nos. 3,717,634 and 4,182,763

MJL8-4270R2

Mead Johnson
PHARMACEUTICALS
A Bristol-Myers Squibb Company
Princeton, New Jersey 08543
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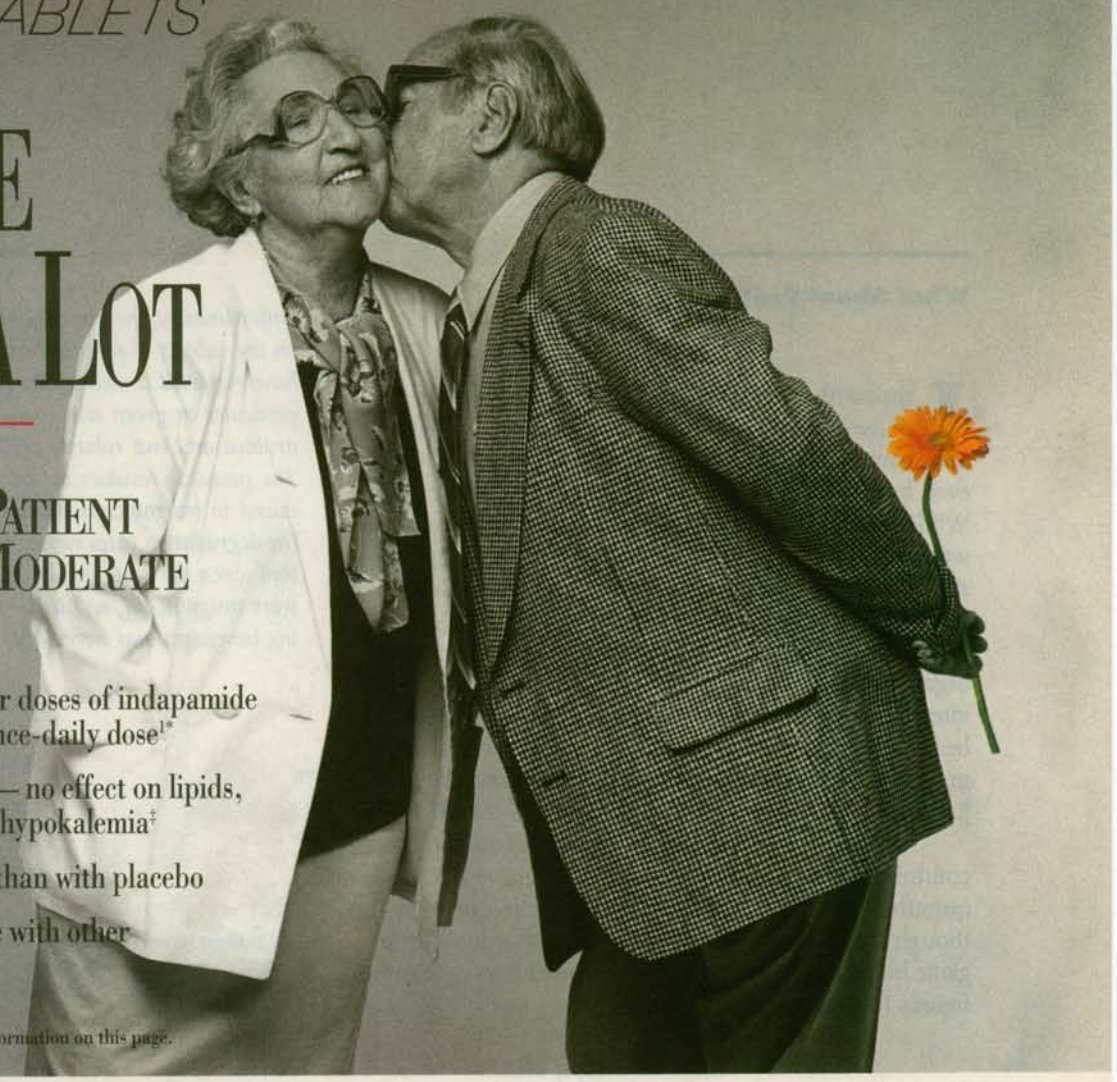
NEW LOW-DOSE

LOZOL® 1.25 MG

INDAPAMIDE TABLETS



A LITTLE MEANS A LOT

TO THE OLDER PATIENT WITH MILD TO MODERATE HYPERTENSION

Efficacy comparable to higher doses of indapamide with the benefits of a lower once-daily dose[1]*

Favorable metabolic profile† — no effect on lipids, only 2% incidence of clinical hypokalemia‡

Less patient discontinuation than with placebo

Side-effect profile compatible with other antihypertensive agents

Please see brief summary of prescribing information on this page.

LOZOL® (indapamide) 1.25 mg and 2.5 mg tablets
BRIEF SUMMARY
INDICATIONS: LOZOL (indapamide) is indicated for the treatment of hypertension, alone or in combination with other antihypertensive drugs, and for the treatment of salt and fluid retention associated with congestive heart failure.
Usage in Pregnancy: See PRECAUTIONS.
CONTRAINDICATIONS: Anuria, hypersensitivity to indapamide or other sulfonamide-derived drugs.
WARNINGS: Infrequent cases of severe hyponatremia, accompanied by hypokalemia, have been reported with 2.5 mg and 5.0 mg indapamide primarily in elderly females. Symptoms were reversed by electrolyte replenishment. Hyponatremia considered possibly clinically significant (<125 mEq/L) has not been observed in clinical trials with the 1.25 mg dosage (see PRECAUTIONS). Hypokalemia occurs commonly with diuretics (**see ADVERSE REACTIONS, hypokalemia**), and electrolyte monitoring is essential. In general, diuretics should not be given with lithium.
PRECAUTIONS: Perform serum electrolyte determinations at appropriate intervals, especially in patients who are vomiting excessively or receiving parenteral fluids, in patients subject to electrolyte imbalance, or in patients on a salt-restricted diet. In addition, patients should be observed for clinical signs of fluid or electrolyte imbalance, such as hyponatremia, hypochloremic alkalosis, or hypokalemia. The risk of hypokalemia secondary to diuresis and natriuresis is increased with larger doses, with brisk diuresis, with severe cirrhosis, and with concomitant use of corticosteroids or ACTH. Interference with adequate oral intake of electrolytes will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis, such as increased ventricular irritability.
Dilutional hyponatremia may occur in edematous patients; appropriate treatment is usually water restriction. In actual salt depletion, appropriate replacement is the treatment of choice. Chloride deficit is usually mild, not requiring specific treatment except in extraordinary circumstances (liver, renal disease).
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. A mean increase in glucose of 6.47 mg/dL was observed in patients treated with indapamide 1.25 mg, which was not considered clinically significant in these trials. Serum concentrations of glucose should be monitored routinely during treatment with indapamide.
Calcium excretion is decreased by diuretics pharmacologically related to indapamide. After six to eight weeks of indapamide 1.25 mg treatment and in long-term studies of hypertensive patients with higher doses of indapamide, however, serum concentrations of calcium increased only slightly with indapamide. Indapamide may decrease serum PBI levels without signs of thyroid disturbance. Complications of hyperparathyroidism have not been seen. Discontinue before tests of parathyroid function are performed.
Thiazides have exacerbated or activated systemic lupus erythematosus. Consider this possibility with indapamide.
DRUG INTERACTIONS: LOZOL may add to or potentiate the action of other antihypertensive drugs. The antihypertensive effect of the drug may be enhanced in the postsympathectomized patient. Indapamide may decrease arterial responsiveness to norepinephrine, but this does not preclude the use of norepinephrine.
In mouse and rat lifetime carcinogenicity studies, there were no significant differences in the incidence of tumors between the indapamide-treated animals and the control groups.
Pregnancy Category B: Diuretics cross the placental barrier and appear in cord blood. Indapamide should be used during pregnancy only if clearly needed. Use may be associated with fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse effects that have occurred in adults. It is not known whether this drug is excreted in human milk. If use of this drug is deemed essential, the patient should stop nursing.
ADVERSE REACTIONS: Most adverse effects have been mild and transient. From Phase II/III placebo-controlled studies with indapamide 1.25 mg, adverse reactions with ≥5% cumulative incidence: headache, infection, pain, back pain, dizziness, rhinitis; <5% cumulative incidence: asthenia, flu syndrome, abdominal pain, chest pain, constipation, diarrhea, dyspepsia, nausea, peripheral edema, nervousness, hypertonia, cough, pharyngitis, sinusitis, conjunctivitis. All other clinical adverse reactions occurred at an incidence of <1%. In controlled clinical trials of six to eight weeks in duration, 20% of patients receiving indapamide 1.25 mg, 61% of patients receiving indapamide 5.0 mg, and 80% of patients receiving indapamide 10.0 mg had at least one potassium value below 3.4 mEq/L. In the indapamide 1.25 mg group, about 40% of those patients who reported hypokalemia as a laboratory adverse event returned to normal serum potassium values without intervention. Hypokalemia with concomitant clinical signs or symptoms occurred in 2% of patients receiving indapamide 1.25 mg. From Phase II placebo-controlled studies and long-term controlled clinical trials with LOZOL 2.5 mg or 5.0 mg, adverse reactions with ≥ 5% cumulative incidence: headache, dizziness, fatigue, weakness, loss of energy, lethargy, tiredness or malaise, muscle cramps or spasm or numbness of the extremities, nervousness, tension, anxiety, irritability or agitation; <5% cumulative incidence: lightheadedness, drowsiness, vertigo, insomnia, depression, blurred vision, constipation, nausea, vomiting, diarrhea, gastric irritation, abdominal pain or cramps, anorexia, orthostatic hypotension, premature ventricular contractions, irregular heart beat, palpitations, frequency of urination, nocturia, polyuria, rash, hives, pruritus, vasculitis, impotence or reduced libido, rhinorrhea, flushing, 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. In the indapamide 2.5 mg group, over 50% of those patients returned to normal serum potassium values without intervention. Other adverse reactions reported with antihypertensive/diuretics are intrahepatic cholestatic jaundice, sialadenitis, xanthopsia, photosensitivity, purpura, bullous eruptions, Stevens-Johnson syndrome, necrotizing 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 controlled room temperature, 15°-30°C (59°-86°F). Avoid excessive heat. Dispense in tight containers as defined in USP.
See product circular for full prescribing information.
Revised: April 1993

* In a controlled clinical trial, at 8 weeks the change in supine diastolic BP with 5 mg of indapamide was -10.8 mm Hg vs. -8.8 mm Hg with LOZOL 1.25 mg.

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

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

Reference: 1. Data on file, Rhône-Poulenc Rorer Pharmaceuticals Inc.

RHÔNE-POULENC RORER

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

LZ70M793(1)A 7/93 FC# 93-R70

STOP THE PAIN. NOT THE PATIENT.

AN ANALGESIC NSAID FOR LIMITED-DURATION USE

TORADOL®

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

(KETOROLAC TROMETHAMINE)

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

THE ANALGESIC NSAID ALTERNATIVE TO NARCOTICS.

FOR MODERATE TO SEVERE PAIN

TORADOL IM

When you would use injectable narcotics for short-term management of pain

Loading dose: 30 mg IM or 60 mg IM

Maintenance dose: 15 mg IM or 30 mg IM q6h, respectively

Duration of use: TORADOL IM is only recommended for short-term therapy (not over 5 days), because the frequency and severity of adverse reactions may increase with longer use at recommended doses.

Maximum daily dose: 150 mg on first day, 120 mg/day thereafter

Dosage adjustments: The lower end of the dosage range is recommended for patients under 50 kg (110 pounds) of body weight, for patients over 65 years of age, and for patients with reduced renal function.

TRANSITION DOSING FROM TORADOL IM TO TORADOL ORAL

When you would use Vicodin or Tylenol #3 for follow-on therapy of limited duration

For patients whose last IM dose was **30 mg,** give two (2) 10 mg tablets of TORADOL ORAL as a **first oral dose,** followed by one (1) 10 mg tablet every 4 to 6 hours (see Follow-on Dosing of TORADOL ORAL below).

For patients whose last IM dose was **15 mg**, give one (1) 10 mg tablet of TORADOL ORAL, followed by one (1) 10 mg tablet every 4 to 6 hours (see Follow-on Dosing of TORADOL ORAL below).

Maximum combined daily dose: Not to exceed 120 mg on day of transition, including a maximum of 40 mg orally.

FOLLOW-ON DOSING: TORADOL ORAL

One (1) 10 mg tablet q4–6h prn; not to exceed four (4) tablets/day. Doses of 10 mg q.i.d. are not recommended for chronic use.

Duration of use: TORADOL ORAL is indicated for limited-duration use (average 5–14 days). TORADOL ORAL is not recommended for long-term use in patients with chronic painful conditions because of the possibility of increased frequency and severity of GI and other adverse reactions.

Maximum daily dose: 40 mg

NONOPIOID. NONADDICTIVE. NONSCHEDULED.

TORADOL® IM INJECTION 15, 30, 60 MG ORAL TABLETS 10 MG
(KETOROLAC TROMETHAMINE)

AN ANALGESIC NSAID FOR LIMITED-DURATION USE

The most logical use of TORADOL ORAL is in patients who have benefited from TORADOL IM without limiting side effects. They can be continued on analgesic treatment with TORADOL ORAL. It is recommended to use the lowest effective dose of TORADOL IM at the transition to TORADOL ORAL and to continue treatment with TORADOL ORAL for as short a time as possible.

The most frequently reported side effects 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 q.i.d. were as follows: gastrointestinal pain 13%, nausea 12%, dyspepsia 12%, and headache 17%.

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 anaphylactic reactions.

PRN narcotics may be added for "breakthrough" pain. TORADOL IM and narcotics should not be administered in the same syringe.

Please see brief summary of prescribing information on following pages.

SYNTEX | Roche

STOP THE PAIN. NOT THE PATIENT.

TORADOL® IM INJECTION 15, 30, 60 MG ORAL TABLETS 10 MG (KETOROLAC TROMETHAMINE)

AN ANALGESIC NSAID FOR LIMITED-DURATION USE

The most frequently reported side effects are gastrointestinal (dyspepsia, nausea, and GI pain) and CNS (headache).

Before prescribing TORADOL, please consult full prescribing information.

TORADOL® IM and TORADOL® ORAL (ketorolac tromethamine)

BRIEF SUMMARY

DESCRIPTION

TORADOL (ketorolac tromethamine) 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.

PHYSICIANS SHOULD CAREFULLY WEIGH THE POTENTIAL RISKS AND BENEFITS OF TORADOL ORAL USE ON A LONG-TERM BASIS. PATIENTS SHOULD BE INSTRUCTED TO WATCH FOR SIGNS OF SERIOUS GI ADVERSE EVENTS AND THEY SHOULD BE MONITORED MORE CLOSELY THAN IF THEY WERE ON ANOTHER NSAID.

Individualization of Dosage: *Suggestions for using TORADOL IM on a prn schedule.*

Since the half-life of TORADOL is approximately 6 hours, an assessment of the size of a repeat dose can be based on the duration of pain relief from the previous dose. For example, if pain returns within 3 to 5 hours of a maintenance dose (15 or 30 mg), the next dose could be increased by up to 50% [Note: The recommended maximum total daily dose is 120 mg (150 mg on the first day); an alternative would be to use morphine or meperidine concomitantly (see INDICATIONS and DRUG INTERACTIONS)]. Alternatively, if pain does not return for 8 to 12 hours, the next dose could be decreased by as much as 50%, or the dosage interval could be increased to 8 to 12 hours.

Note: The initial intramuscular loading dose (30 or 60 mg) should be given only once, unless therapy has been interrupted for 3 half-lives (15-40 hours, see half-life of TORADOL IM in Table in CLINICAL PHARMACOLOGY section of full prescribing information).

TORADOL IM is only recommended for short-term therapy (not over 5 days), because adverse reactions may increase with longer use at recommended doses (see WARNINGS and PRECAUTIONS).

The lower end of the dosage range is recommended for patients under 50 kg (110 pounds) of body weight, for patients over 65 years of age, and for patients with reduced renal function (see CLINICAL PHARMACOLOGY and PRECAUTIONS sections of full prescribing information).

If management by regular scheduled doses is elected, see DOSAGE AND ADMINISTRATION section of full prescribing information for dosing recommendations.

The most logical use of TORADOL ORAL is in patients who have benefited from TORADOL IM without limiting side effects. They can be continued on analgesic treatment with TORADOL ORAL (see DOSAGE AND ADMINISTRATION–Transition from TORADOL IM to TORADOL ORAL). It is recommended to use the lowest effective dose of TORADOL IM at the transition to TORADOL ORAL and to continue treatment with TORADOL ORAL for as short a time as possible (see WARNINGS and ADVERSE REACTIONS).

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), admadministration 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 intraoperatively. 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.

TORADOL® IM and TORADOL® ORAL (ketorolac tromethamine)

Practical Dermatology

by Beth G. Goldstein and Adam O. Goldstein, 328 pages, 211 illus, $51.95, ISBN 0-8151-3542-4, St Louis, Mo, Mosby–Year Book Inc, 1992.

Perhaps not a day goes by that a family physician does not encounter a patient with a rash. With common complaints of red spots, scaly skin, or terrible itching, dermatology is an intricate part of family medicine.

Practical Dermatology, by Beth and Adam Goldstein (she is a dermatologist and he, a family physician), is a book that will fill a void on many clinicians' bookshelves. The book is divided into four parts. Part I discusses the art of dermatology. This includes the dermatologic basics (terminology, differential diagnoses, and pitfalls in diagnoses), dermatologic therapies (topical agents, corticosteroid agents, patient-centered therapy, and pitfalls of treatment), diagnostic procedures (potassium hydroxide preparation, fungal culture, scabies test, Tzanck smear, Wood's light examination, cryosurgery, curettage, electrodesiccation, and shave and punch biopsies, as well as shave, punch, snip, elliptical, and cyst excisions), and preventive dermatology (occupational and environmental).

Discussions of the common skin dermatoses are found in part II. The authors also include discussions of 110 dermatologic disorders and 25 skin manifestations of systemic disease. The sections are logically arranged in outline order. Each includes classic description (distribution, primary, secondary), diagnosis, differential diagnosis, treatment, and prevention.

The authors have used more than 125 color illustrations and 200 figures to help the reader understand the physical presentation of the dermatologic findings associated with the clinical disorders.

The sections on treatment include common sense instructions to promote symptomatic relief and resolution of the problem. Pharmacologic options, techniques for surgical intervention, and preventive steps are presented in a straightforward manner.

In addition, this book contains special sections on skin disorders of pregnancy, geriatric patients, acquired immunodeficiency syndrome, the newborn, and the cutaneous manifestations of systemic diseases.

A thoughtful and useful addition is the appendix, which includes patient education handouts on 14 of the most commonly encountered dermatologic problems. The publisher has granted permission to reproduce these handouts for distribution to one's patients.

In summary, this book is very easy to use and will be quite helpful as a rapid reference source for most commonly and some not so commonly encountered dermatologic problems. Collected from the files of two medical schools and two practices, the photographs are excellent. The common-sense approaches to therapy and prevention contain many of the practical pearls of dermatology that can make a family physician's practice more successful and rewarding. This book would make an excellent basic text and/or reference text for medical students, residents, faculty, and prac-

Section Editor, Michael L. Adler, MD, Department of Family and Community Medicine, Bowman Gray School of Medicine, Winston-Salem, NC.

For pain/inflammation

Rx Anaprox® DS 550 MG TABLETS

Anaprox® 275 MG TABLETS

(NAPROXEN SODIUM)

SYNTEX

SYNTEX PUERTO RICO, INC.
HUMACAO, PR 00661

As with other NSAIDs, the most frequent complaints are gastrointestinal. See Warnings, Precautions, and Adverse Reactions sections of prescribing information. Please see adjacent page for brief summary of prescribing information.

 811-J2-557-92

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 dose 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)

HELP PREVENT HEART ATTACK WITH A STROKE.

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

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

American Heart Association

This space provided as a public service. ©1992, American Heart Association

Ismo® (isosorbide mononitrate) 20 mg tablets

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

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

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

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

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

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

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

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

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

Nitrates may aggravate angina caused by hypertrophic cardiomyopathy.

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

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

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

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

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

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

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

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

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

PEDIATRIC USE Safety and effectiveness have not been established.

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

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

*Some individuals discontinued for multiple reasons

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

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

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

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

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

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

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

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

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

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

A·H·ROBINS | BOEHRINGER MANNHEIM PHARMACEUTICALS | WYETH-AYERST LABORATORIES

60312P

Ismo®

20 mg tablets

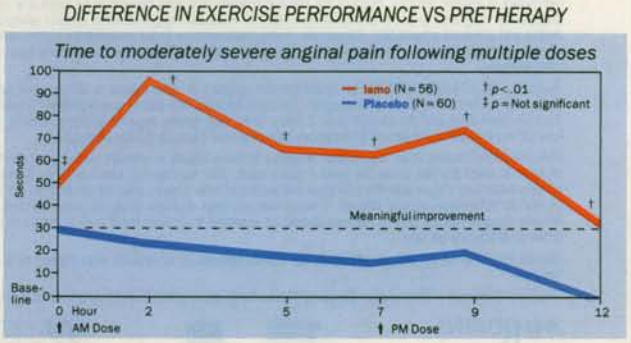
(isosorbide mononitrate)

ACTIVITY YOU CAN COUNT ON

Antianginal activity for at least 12 hours*

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

DIFFERENCE IN EXERCISE PERFORMANCE VS PRETHERAPY



Baseline = 7 min 3 sec

(Adapted from Protocol 12)[1]

Predictable pharmacokinetic profile

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

Helps get active patients active again

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

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

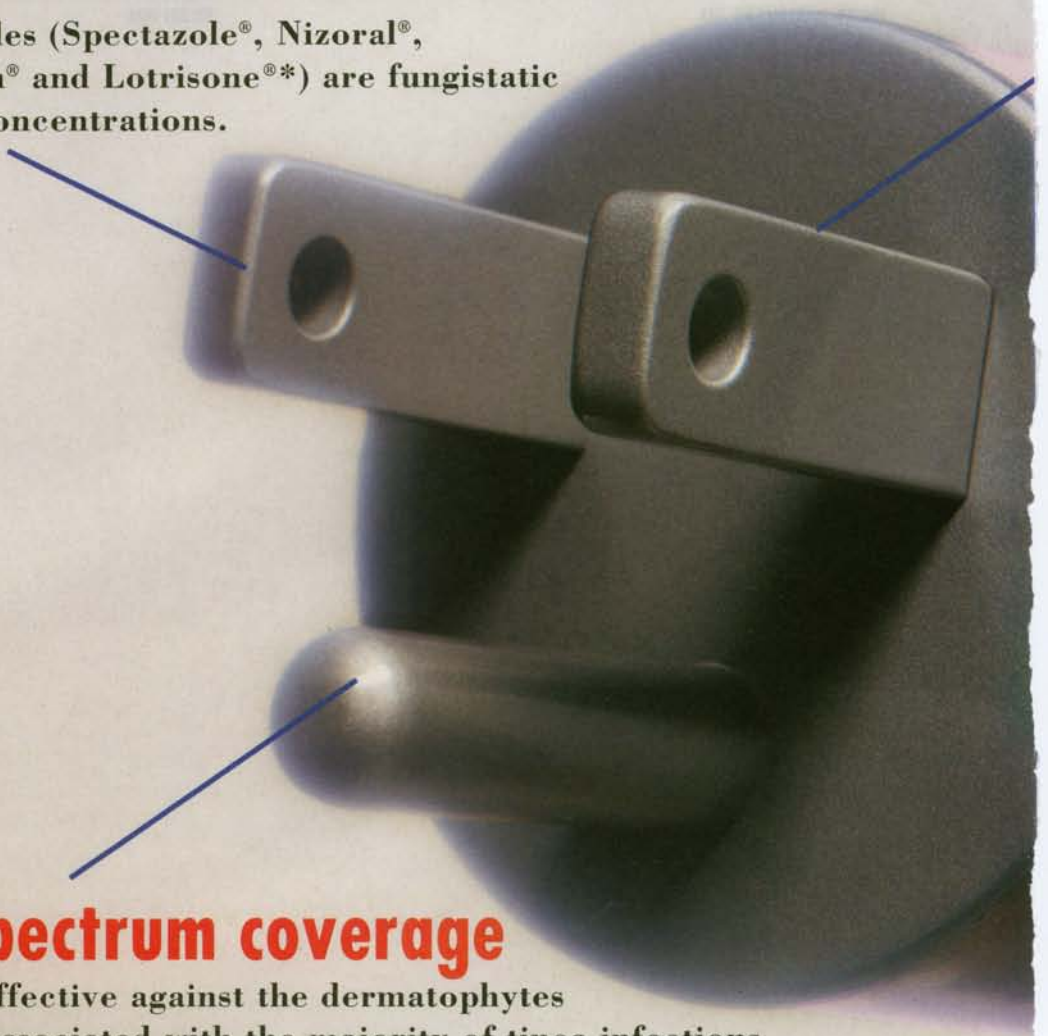
References: 1. Data on file, Wyeth-Ayerst Laboratories, Protocol 12. **2.** Abshagen U: Overview of the pharmacokinetics of isosorbide-5-mononitrate. In Julian DG, Rittinghausen R, Überbacher HJ, eds. Mononitrate II. New York: Springer-Verlag; 1987:pp 28-36.

Please see brief summary of prescribing information on adjacent page.

HARNESS THE TRIPLE THE POTENT

1. Fungicidal action

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



3. Broad spectrum coverage

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

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

The Standard of Skin Care

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Irvine, CA 92715

For a copy of "Diagnosis and Treatment of Fungal Infe

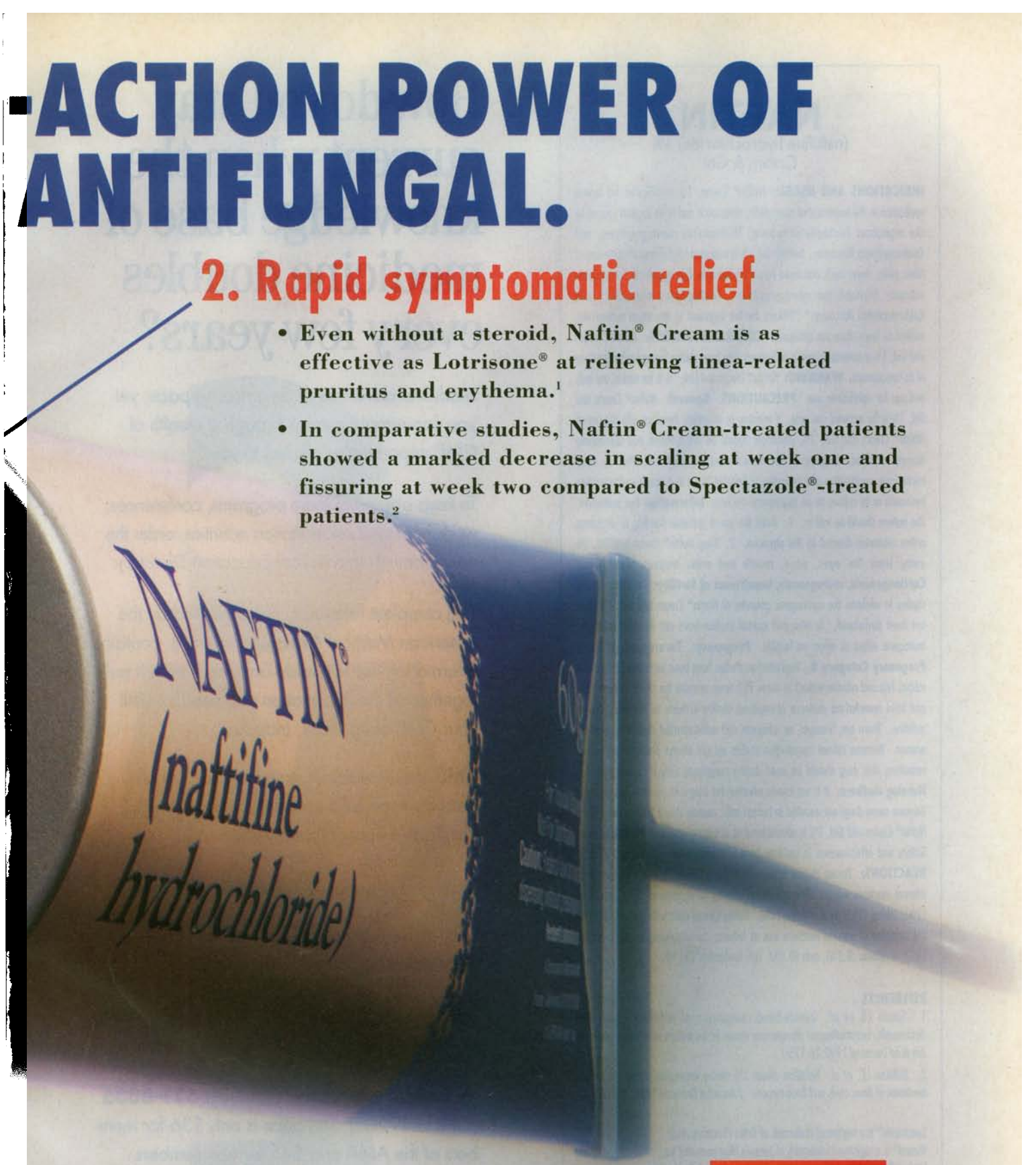
**In vitro data*, clinical significance unknown. A low incidence of irritation and

Please see adjacent page for brief summary of pres

-ACTION POWER OF ANTIFUNGAL.

2. Rapid symptomatic relief

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



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

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

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

NAFTIN®

(naftifine hydrochloride) 1%
Cream & Gel

INDICATIONS AND USAGE: Naftin® Cream, 1% is indicated for topical application in the treatment of tinea pedis, tinea cruris and tinea corporis caused by the organisms *Trichophyton rubrum, Trichophyton mentagrophytes*, and *Epidermophyton floccosum*. Naftin® Gel 1% is indicated for the topical treatment of tinea pedis, tinea cruris and tinea corporis caused by the organisms *Trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton tonsurans** and *Epidermophyton floccosum.** *Efficacy for this organism in this organ system was studied in fewer than ten infections. **CONTRAINDICATIONS:** Naftin® Cream and Gel, 1% is contraindicated in individuals who have shown hypersensitivity to any of its components. **WARNING:** Naftin® Cream and Gel, 1% is for topical use only and not for ophthalmic use. **PRECAUTIONS**: **General:** Naftin® Cream and Gel, 1% is for external use only. If irritation or sensitivity develops with the use of Naftin® Cream and Gel, 1%, treatment should be discontinued and appropriate therapy instituted. Diagnosis of the disease should be confirmed either by direct microscopic examination of a mounting of infected tissue in a solution of potassium hydroxide or by culture on an appropriate medium. **Information for patients**: The patient should be told to: 1. Avoid the use of occlusive dressing or wrappings unless otherwise directed by the physician. 2. Keep Naftin® Cream and Gel, 1% away from the eyes, nose, mouth and other mucous membranes. **Carcinogenesis, mutagenesis, impairment of fertility:** Long-term animal studies to evaluate the carcinogenic potential of Naftin® Cream and Gel, 1% have not been performed. *In vitro* and animal studies have not demonstrated any mutagenic effect or effect on fertility. **Pregnancy: Teratogenic Effects: Pregnancy Category B.** Reproduction studies have been performed in rats and rabbits (via oral administration) at doses 150 times or more the topical human dose and have revealed no evidence of impaired fertility or harm to the fetus due to naftifine. There are, however, 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:** 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 Naftin® Cream and Gel, 1% is administered to a nursing woman. **Pediatric use:** Safety and effectiveness in children have not been established. **ADVERSE REACTIONS:** During clinical trials with Naftin® Cream, 1%, the incidence of adverse reactions was as follows: burning/stinging (6%), dryness (3%), erythema (2%), itching (2%), local irritation (2%). During clinical trials with Naftin® Gel, 1%, the incidence of adverse reactions was as follows: burning/stinging (5%), itching (1%), erythema (0.5%), rash (0.5%), skin tenderness (0.5%).

REFERENCES

1. Smith EB *et al.* Double-blind comparison of naftifine cream and clotrimazole/betamethasone dipropionate cream in the treatment of tinea pedis. *J Am Acad Dermatol* 1992;26:125-7.

2. Millikan LE, *et al.* Naftifine cream 1% versus econazole cream 1% in the treatment of tinea cruris and tinea corporis. *J Am Acad Dermatol* 1988; 18:52-6.

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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.
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- The 8th most frequently prescribed medication in America.[2]

vicodin ES® (III)

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

Extra strength pain relief you can phone in.

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

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

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WHY CONSIDER TENORMIN BEFORE ALL OTHER BETA BLOCKERS?

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

I.V. INJECTION/TABLETS

TENORMIN®

(atenolol)

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

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

See adjacent page for brief summary of prescribing information.

I.V. INJECTION/TABLETS

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

(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT.)

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

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

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

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

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

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

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

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

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, the lowest possible dose of TENORMIN should be used with therapy initiated at 50 mg and a beta$_2$-stimulating agent (bronchodilator) should be made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Reasons for Reduced Dosage

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

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

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

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

Hematologic: Agranulocytosis.

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

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

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Erythematous rash, Raynaud's phenomenon.

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

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

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

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

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

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

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

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

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

BRONCHOSPASM: A beta$_2$ stimulant such as isoproterenol or terbutaline and/or aminophylline.

HYPOGLYCEMIA: Intravenous glucose.

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

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

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

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

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

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

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

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

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

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

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

No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 mL/min/1.73m^2. Accumulation of atenolol and prolongation of its half-life were studied in subjects with creatinine clearance between 5 and 105 mL/min. Peak plasma levels were significantly increased in subjects with creatinine clearances below 30 mL/min.

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

Creatinine Clearance (mL/min/1.73m^2)	Atenolol Elimination Half-Life (h)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	25 mg daily

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

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

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

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

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

HOW SUPPLIED

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

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

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

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

TENORMIN I.V. Injection

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

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

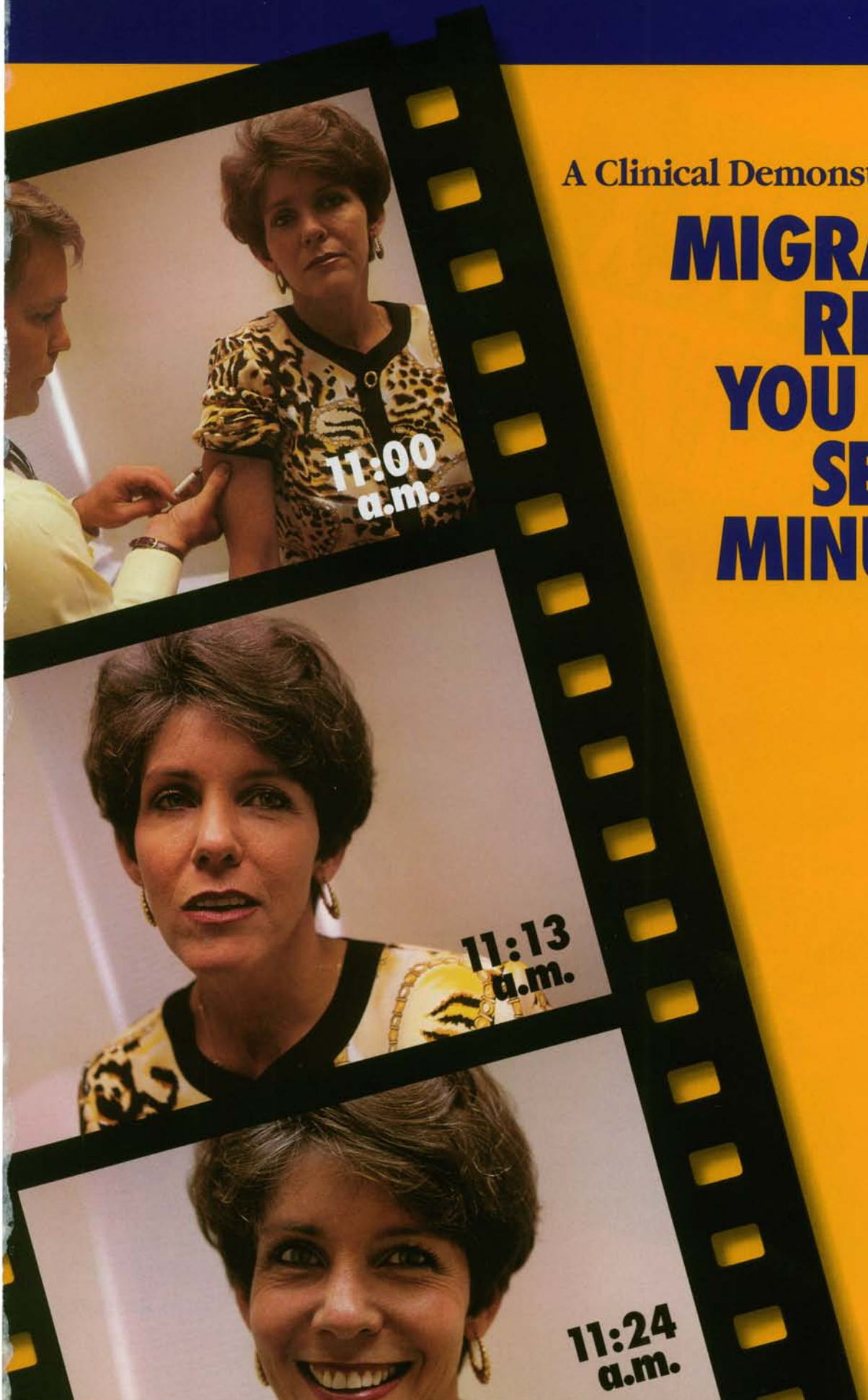
REV Y 03/92

ZENECA Pharmaceuticals
A Business Unit of ZENECA Inc.
Wilmington, Delaware 19897 USA

FSA-1511 ICI-2870R

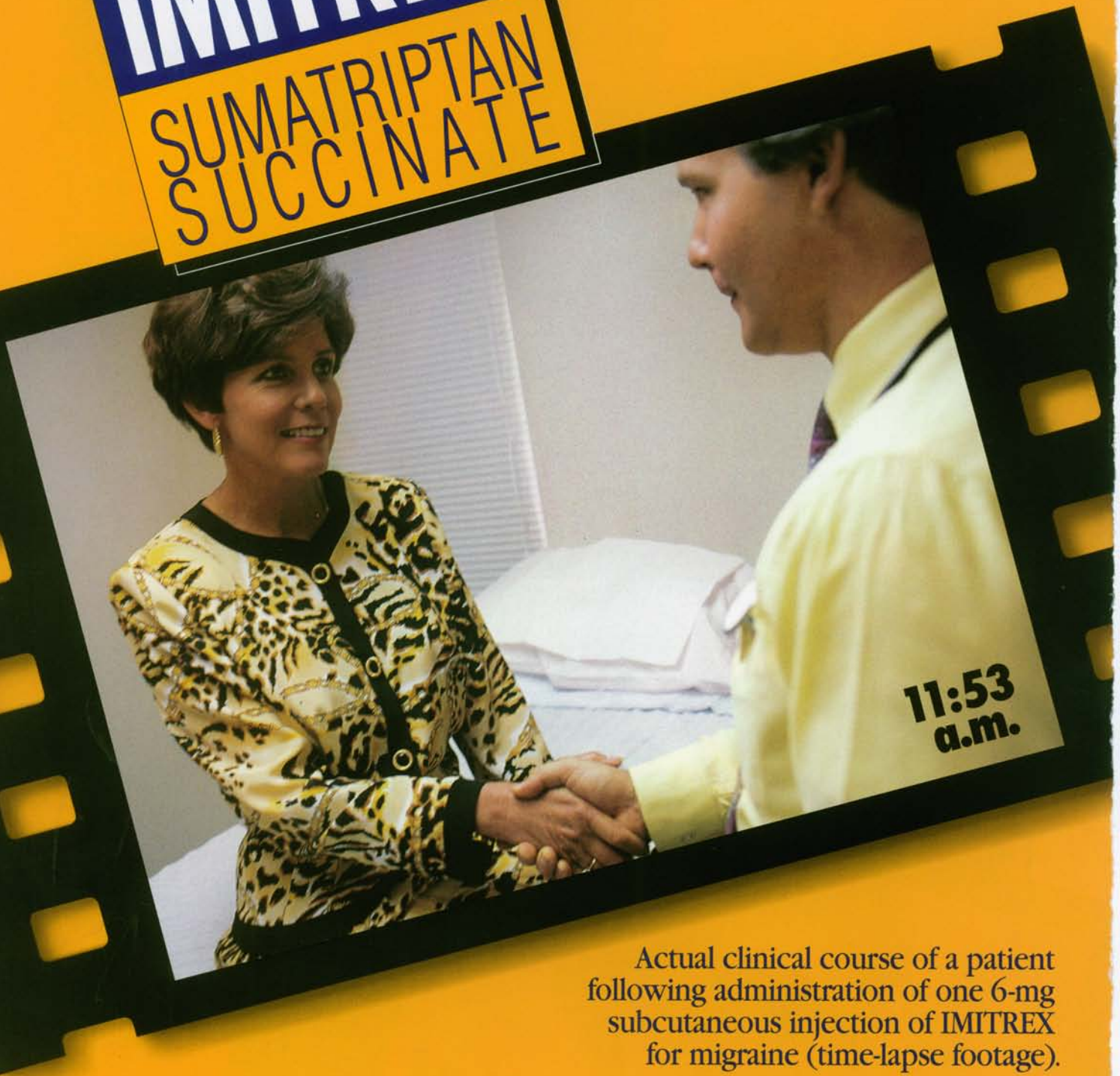
A Clinical Demonstration of

MIGRAINE RELIEF YOU CAN SEE IN MINUTES



CERENEX PHARMACEUTICALS INTRODUCES

NEW SUBCUTANEOUS IMITREX™ SUMATRIPTAN SUCCINATE



Actual clinical course of a patient following administration of one 6-mg subcutaneous injection of IMITREX for migraine (time-lapse footage).

MIGRAINE RELIEF THAT CAN CHANGE PATIENTS' LIVES

IMITREX is the first highly specific 5-HT_1 receptor agonist—offering a profile of relief unlike any other migraine therapy.

Relief that begins within 10 minutes.[1,2]

Relief any time IMITREX is taken during the attack.[1,3,4]

Relief of the total symptom complex: pain, nausea, vomiting, and light and sound sensitivity.[1-4]

Relief of the disability caused by migraine.[1-4]

Relief without sedation.

Relief in a simple, convenient dose: one 6-mg subcutaneous injection.*

Relief within reach for patients: The IMITREX™ SELFdose System—a push-button autoinjector with single-dose, prefilled syringes.

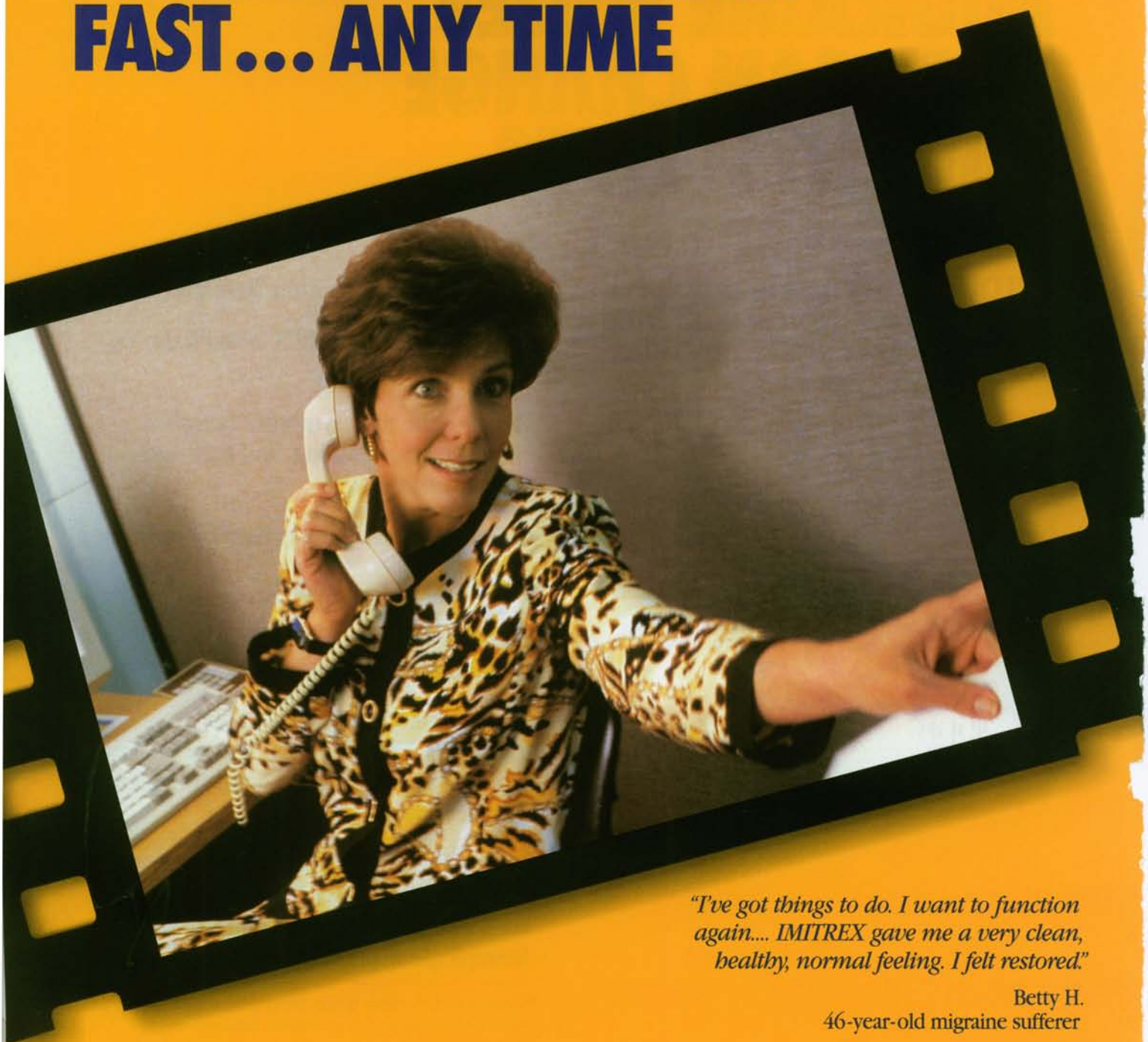
Relief of migraine attacks with or without aura. (IMITREX should not be administered to patients with basilar or hemiplegic migraine.)

*Maximum daily dose is two 6-mg subcutaneous injections (minimum 1-hour interval between doses). No clear benefit is associated with the administration of a second 6-mg dose in patients who have failed to respond to a first injection.

Please consult Brief Summary of Prescribing Information on the last page of this advertisement.

CERENEX PHARMACEUTICALS

RELIEF OF THE TOTAL SYMPTOM COMPLEX FAST... ANY TIME



"I've got things to do. I want to function again.... IMITREX gave me a very clean, healthy, normal feeling. I felt restored."

Betty H.
46-year-old migraine sufferer

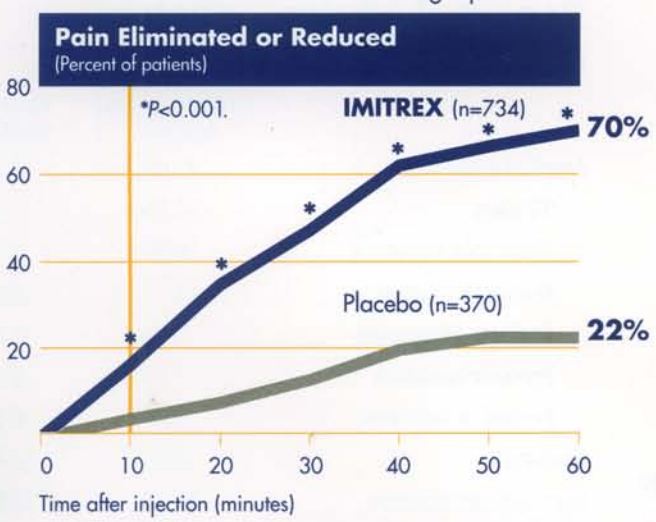
INTRODUCES

NEW SUBCUTANEOUS IMITREX™ SUMATRIPTAN SUCCINATE

MIGRAINE RELIEF THAT CAN CHANGE PATIENTS' LIVES

IMITREX significantly relieves pain, beginning 10 minutes after injection.[1,2]

Percent of Patients With Moderate to Severe Pain Eliminated or Reduced After One 6-mg Injection[2]



Data are from a randomized, double-blind, placebo-controlled, multicenter study of 1,104 migraine patients receiving injection with IMITREX 6 mg or placebo. Pain relief was defined as reduction of moderate or severe headache pain (grade 2 or 3) to mild or no headache pain (grade 1 or 0).[2]

IMITREX relieves nausea, vomiting, and light and sound sensitivity—helping patients get back to work, back to their lives.[1-4]

IMITREX eliminated nausea, photophobia, and disability due to migraine significantly better than placebo—beginning within 20 minutes after injection ($P<0.001$; n=1,104).[2]

IMITREX works at any time during the attack.[1,3,4]

Its efficacy is unchanged whether administered early or later in the migraine episode.[1,3,4]

Please consult Brief Summary of Prescribing Information on the last page of this advertisement.

RELIEF WITHOUT COMPROMISE

IMITREX is highly selective.

IMITREX is nonsedating.

There is no evidence of interactions between IMITREX and prophylactic migraine medications (verapamil, amitriptyline, and propranolol).

Cardiovascular considerations

IMITREX is contraindicated in patients with ischemic heart disease, symptoms or signs consistent with ischemic heart disease, or Prinzmetal's angina because of the potential to cause coronary vasospasm. IMITREX is contraindicated in patients with uncontrolled hypertension because it can give rise to increases in blood pressure (usually small).

Although serious coronary events are extremely rare, consideration should be given to administering the first dose of IMITREX in-office to patients in whom unrecognized coronary disease is comparatively likely.

Pregnancy category C

There are no adequate and well-controlled studies in pregnant women; IMITREX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (Please see Precautions.)

Worldwide clinical experience

IMITREX has been utilized by over 6,000 patients, treating more than 10,000 attacks in well-controlled clinical trials.[5]

Reported adverse events are generally mild and transient.

	IMITREX (6 mg) (n=547)	Placebo (n=370)
Atypical sensations	42.0%	9.2%
Tingling	13.5%	3.0%
Warm/hot sensation	10.8%	3.5%
Burning sensation	7.5%	0.3%
Feeling of heaviness	7.3%	1.1%
Pressure sensation	7.1%	1.6%
Feeling of tightness	5.1%	0.3%
Flushing	6.6%	2.4%
Injection-site reaction	58.7%	23.8%
Dizziness/Vertigo	11.9%	4.3%

Most adverse events were mild and resolved spontaneously within 10 to 30 minutes.[3]

Withdrawals due to adverse events are comparable to those seen with placebo (≤3.5% in controlled clinical trials).[2-4]

For a complete listing of side effects, please consult Brief Summary of Prescribing Information on the last page of this advertisement.

INTRODUCES

NEW SUBCUTANEOUS IMITREX™ SUMATRIPTAN SUCCINATE

MIGRAINE RELIEF THAT CAN CHANGE PATIENTS' LIVES

RELIEF WITHIN REACH FOR PATIENTS

The IMITREX™ SELFdose System: a push-button autoinjector with single-dose, prefilled syringes.

Allows patients to self-administer IMITREX whenever and wherever migraine strikes.

High patient acceptance.[4]

— 92% of patients who self-administered IMITREX would be willing to take it again.[5]

Efficacy equivalent to physician-administered IMITREX.[2-4]

For use only by patients for whom a 6-mg dose has been prescribed.

IMITREX offers simple, convenient dosing.

The recommended dose is one 6-mg subcutaneous injection.

If migraine symptoms return, a second 6-mg dose may be administered.

The maximum dose within 24 hours is two 6-mg subcutaneous injections (minimum 1-hour interval between doses).

No clear benefit is associated with the administration of a second 6-mg dose in patients who have failed to respond to a first injection.

Although the recommended dose is 6 mg, if side effects are dose limiting, then lower doses may be used.

IMITREX should not be used within 24 hours of administration of ergotamine-containing preparations.

References: 1. Complete Prescribing Information, IMITREX™ (sumatriptan succinate) Injection. January 1993. **2.** Cady RK et al. Treatment of acute migraine with subcutaneous sumatriptan. *JAMA*.1991;265:2831-2835. **3.** The Subcutaneous Sumatriptan International Study Group. Treatment of migraine attacks with sumatriptan. *N Engl J Med*. 1991;325:316-321. **4.** The Sumatriptan Auto-Injector Study Group. Self-treatment of acute migraine with subcutaneous sumatriptan using an auto-injector device. *Eur Neurol*. 1991;31:323-331. **5.** Data on file, Glaxo Inc.

Please consult Brief Summary of Prescribing Information on the last page of this advertisement.

BRIEF SUMMARY

Imitrex™ (sumatriptan succinate) Injection

For Subcutaneous Use Only.

The following is a brief summary only. Before prescribing, see complete prescribing information in Imitrex™ Injection product labeling.

INDICATIONS AND USAGE: Imitrex™ Injection is indicated for the acute treatment of migraine attacks with or without aura.

Imitrex Injection is not for use in the management of hemiplegic or basilar migraine (see WARNINGS).

Safety and effectiveness have also not been established for cluster headache, which is present in an older, predominantly male population.

CONTRAINDICATIONS: Imitrex™ Injection should not be given intravenously because of its potential to cause coronary vasospasm.

For similar reasons, Imitrex Injection should not be given subcutaneously to patients with ischemic heart disease (angina pectoris, history of myocardial infarction, or documented silent ischemia) or to patients with Prinzmetal's angina. Also, patients with symptoms or signs consistent with ischemic heart disease should not receive Imitrex Injection. Because Imitrex Injection can give rise to increases in blood pressure (usually small), it should not be given to patients with uncontrolled hypertension.

Imitrex Injection should not be used concomitantly with ergotamine-containing preparations.

Imitrex Injection is contraindicated in patients with hypersensitivity to sumatriptan.

WARNINGS:

Imitrex™ Injection should not be administered to patients with basilar or hemiplegic migraine.

Cardiac Events/Coronary Constriction: Serious coronary events following Imitrex Injection can occur but are extremely rare; nonetheless, **consideration should be given to administering the first dose of Imitrex Injection in the physician's office to patients in whom unrecognized coronary disease is comparatively likely** (postmenopausal women; males over 40; patients with risk factors for CAD, such as hypertension, hypercholesterolemia, obesity, diabetes, smokers, and strong family history). **If symptoms consistent with angina occur, electrocardiographic evaluation should be carried out to look for ischemic changes.**

Sumatriptan may cause coronary vasospasm in patients with a history of coronary artery disease who are known to be more susceptible than others to coronary artery vasospasm and rarely in patients without prior history suggestive of coronary artery disease. There were eight patients among the more than 1,900 who participated in controlled trials who sustained clinical events during or shortly after receiving subcutaneous sumatriptan that may have reflected coronary vasospasm. Six of these eight patients had ECG changes consistent with transient ischemia, but without symptoms or signs. Of the eight patients, four had some findings suggestive of coronary artery disease prior to treatment. None of these adverse events was associated with a serious clinical outcome.

There have been rare reports from countries in which Imitrex Injection has been marketed of serious and/or life-threatening arrhythmias, including atrial fibrillation, ventricular fibrillation, ventricular tachycardia and myocardial infarction, as well as marked ischemic ST elevations associated with Imitrex Injection. In addition, there have been rare, but more frequent, reports of chest and arm discomfort thought to represent angina pectoris.

Use in Women of Childbearing Potential: (see PRECAUTIONS)

PRECAUTIONS:

General: Chest, jaw, or neck tightness is relatively common after Imitrex™ Injection, but has only rarely been associated with ischemic ECG changes.

Imitrex Injection may cause mild, transient elevation of blood pressure and peripheral vascular resistance (see CLINICAL PHARMACOLOGY section of the product package insert).

Imitrex Injection should also be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs, such as impaired hepatic or renal function.

Although written instructions are supplied with the autoinjector, patients who are advised to self-administer Imitrex Injection in medically unsupervised situations should receive instruction on the proper use of the product from the physician or other suitably qualified health care professional prior to doing so for the first time.

Information for Patients: See PATIENT INFORMATION at the end of the product package insert for the separate leaflet provided for patients.

Laboratory Tests: No specific laboratory tests are recommended for monitoring patients prior to and/or after treatment with Imitrex Injection.

Drug Interactions: There is no evidence that concomitant use of migraine prophylactic medications has any effect on the efficacy or unwanted effects of sumatriptan. In two phase III trials in the USA, a retrospective analysis of 282 patients who had been using prophylactic drugs (verapamil n=63, amitriptyline n=57, propranolol n=94, for 45 other drugs n=123) were compared to those who had not used prophylaxis (n=452). There were no differences in relief rates at 60 minutes postdose for Imitrex Injection, whether or not prophylactic medications were used. There were also no differences in overall adverse event rates between the two groups.

Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine and sumatriptan within 24 hours of each other should be avoided (see CONTRAINDICATIONS).

Drug/Laboratory Test Interactions: Imitrex Injection is not known to interfere with commonly employed clinical laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 104-week lifetime study in rats given sumatriptan by oral gavage, serum concentrations achieved were dose related, ranging at the low dose from approximately twice the peak concentration of the drug after the recommended human subcutaneous dose of 6 mg to more than 100 times this concentration at the high dose. There was no evidence of an increase in tumors considered to be related to sumatriptan administration.

In a 78-week study in which mice received sumatriptan continuously in drinking water, there was no evidence for an increase in tumors considered to be related to sumatriptan administration. That study, however, did not use the maximum tolerated dose and therefore did not fully explore the carcinogenic potential of Imitrex™ (sumatriptan succinate) Injection in the mouse.

A segment I rat fertility study by the subcutaneous route has shown no evidence of impaired fertility.

Pregnancy: ***Pregnancy Category C:*** Sumatriptan has been shown to be embryolethal in rabbits when given in daily doses producing plasma levels 3-fold higher than those attained following a 6-mg subcutaneous injection (i.e., recommended dose) to humans. There is no evidence that establishes that sumatriptan is a human teratogen; however, there are no adequate and well-controlled studies in pregnant women. Imitrex Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In assessing this information, the following additional findings should be considered.

Embryolethality: When given intravenously to pregnant rabbits daily throughout the period of organogenesis, sumatriptan caused embryolethality at doses at or close to those producing maternal toxicity. The mechanism of the embryolethality is not known. At these doses, peak concentrations of drug in plasma were more than 3-fold higher than the range observed in humans after the recommended subcutaneous dose of 6 mg.

The intravenous administration of sumatriptan to pregnant rats throughout organogenesis at doses producing plasma concentrations more than 50 times those seen after the recommended subcutaneous human dose did not cause embryolethality. In a study of pregnant rats given subcutaneous sumatriptan daily prior to and throughout pregnancy, there was no evidence of increased embryo/fetal lethality.

Teratogenicity: Term fetuses from Dutch Stride rabbits treated during organogenesis with oral sumatriptan exhibited an increased incidence of cervicothoracic vascular defects and minor skeletal abnormalities. The functional significance of these abnormalities is not known.

In a study in rats dosed daily with subcutaneous sumatriptan prior to and throughout pregnancy, there was no evidence of teratogenicity.

Studies in rats and rabbits evaluating the teratogenic potential of sumatriptan administered subcutaneously only during organogenesis (standard Segment II studies) have not been performed.

Nursing Mothers: Sumatriptan is excreted in breast milk in animals. No data exist in humans. Therefore, caution should be exercised when considering the administration of Imitrex Injection to a nursing woman.

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

Use in the Elderly: The safety and effectiveness of Imitrex Injection in individuals over age 65 have not been systematically evaluated. However, the pharmacokinetic disposition of Imitrex Injection in the elderly is similar to that seen in younger adults. No unusual adverse, age-related phenomena have been identified in patients over the age of 60 who participated in clinical trials with Imitrex Injection.

ADVERSE REACTIONS: (see also PRECAUTIONS) Sumatriptan may cause coronary vasospasm in patients with a history of coronary artery disease, known to be susceptible to coronary artery vasospasm, and, very rarely, without prior history suggestive of coronary artery disease.

There have been rare reports from countries in which Imitrex™ Injection has been marketed of serious and/or life-threatening arrhythmias, including atrial fibrillation, ventricular fibrillation, ventricular tachycardia, myocardial infarction, and marked ischemic ST elevations associated with Imitrex Injection (see WARNINGS). More often, there has been chest discomfort that appeared to represent angina pectoris.

Other untoward clinical events associated with the use of subcutaneous Imitrex Injection are: pain or redness at the injection site, atypical sensations (such as sensations of warmth, cold, tingling or paresthesia, pressure, burning, numbness, tightness, all of which may be localized or generalized), flushing, chest symptoms (pressure, pain, or tightness), fatigue, dizziness, and drowsiness. All these untoward effects are usually transient, although they may be severe in some patients. Transient rises in blood pressure soon after treatment have been recorded.

Among patients in clinical trials of subcutaneous Imitrex Injection (n=6,218), up to 3.5% of patients withdrew for reasons related to adverse events.

Incidence in Controlled Clinical Trials: The following table lists adverse events that occurred in two large US, Phase III, placebo-controlled clinical trials following either a single dose of Imitrex Injection or placebo. Only events that occurred at a frequency of 1% or more in Imitrex Injection treatment groups and were at least as frequent as in the placebo group are included in table.

Treatment-Emergent Adverse Experience Incidence in Two Large Placebo-Controlled Clinical Trials: Events Reported by at Least 1% of Imitrex Injection Patients

	Percent of Patients Reporting	
Adverse Event Type	Imitrex Injection 6 mg SC n=547	Placebo n=370
Atypical sensations	42.0	9.2
Tingling	13.5	3.0
Warm/hot sensation	10.8	3.5
Burning sensation	7.5	0.3
Feeling of heaviness	7.3	1.1
Pressure sensation	7.1	1.6
Feeling of tightness	5.1	0.3
Numbness	4.6	2.2
Feeling strange	2.2	0.3
Tight feeling in head	2.2	0.3
Cold sensation	1.1	0.5
Cardiovascular		
Flushing	6.6	2.4
Chest discomfort	4.5	1.4
Tightness in chest	2.7	0.5
Pressure in chest	1.8	0.3
Ear, nose, and throat		
Throat discomfort	3.3	0.5
Discomfort: nasal cavity/sinuses	2.2	0.3
Eye		
Vision alterations	1.1	0.0
Gastrointestinal		
Abdominal discomfort	1.3	0.8
Dysphagia	1.1	0.0
Injection site reaction	58.7	23.8
Miscellaneous		
Jaw discomfort	1.8	0.0
Mouth and teeth		
Discomfort of mouth/tongue	4.9	4.6
Musculoskeletal		
Weakness	4.9	0.3
Neck pain/stiffness	4.8	0.5
Myalgia	1.8	0.5
Muscle cramp(s)	1.1	0.0
Neurological		
Dizziness/vertigo	11.9	4.3
Drowsiness/sedation	2.7	2.2
Headache	2.2	0.3
Anxiety	1.1	0.5
Malaise/fatigue	1.1	0.8
Skin		
Sweating	1.6	1.1

The sum of the percentages cited are greater than 100% because patients may experience more than one type of adverse event. Only events that occurred at a frequency of 1% or more in Imitrex™ (sumatriptan succinate) Injection treatment groups and were at least as frequent as in the placebo groups are included.

Other Events Observed in Association With the Administration of Imitrex Injection: In the paragraphs that follow, the frequency of less commonly reported adverse clinical events are presented. Because the reports cite events observed in open and uncontrolled studies, the role of Imitrex Injection in their causation cannot be reliably determined. Furthermore, variability associated with reporting requirements, the terminology used to describe adverse events, etc., limit the value of the quantitative frequency estimates provided.

Event frequencies are calculated as the number of patients reporting an event divided by the total number of patients (n=6,218) exposed to subcutaneous Imitrex Injection. Given their imprecision, frequencies for specific adverse event occurrences are defined as follows: "infrequent" indicates a frequency estimated as falling between 1/1,000 and 1/100; "rare," a frequency less than 1/1,000.

Cardiovascular: Infrequent were hypertension, hypotension, bradycardia, tachycardia, palpitations, pulsating sensations, various transient electrocardiographic changes (nonspecific ST or T wave changes, prolongation of PR or QTc intervals, sinus arrhythmia, nonsustained ventricular premature beats, isolated junctional ectopic beats, atrial ectopic beats, delayed activation of the right ventricle), and syncope. Rare were pallor, arrhythmia, abnormal pulse, vasodilatation, and Raynaud's syndrome.

Endocrine and Metabolic: Infrequent was thirst. Rare were polydipsia and dehydration.

Eye: Infrequent was irritation of the eye.

Gastrointestinal: Infrequent were gastroesophageal reflux, diarrhea, and disturbances of liver function tests. Rare were peptic ulcer, retching, flatulence/eructation, and gallstones.

Musculoskeletal: Infrequent were various joint disturbances (pain, stiffness, swelling, ache). Rare were muscle stiffness, need to flex calf muscles, backache, muscle tiredness, and swelling of the extremities.

Neurological: Infrequent were mental confusion, euphoria, agitation, relaxation, chills, sensation of lightness, tremor, shivering, disturbances of taste, prickling sensations, paresthesia, stinging sensations, headaches, facial pain, photophobia, and lachrymation. Rare were transient hemiplegia, hysteria, globus hystericus, intoxication, depression, myoclonia, monoplegia/diplegia, sleep disturbance, difficulties in concentration, disturbances of smell, hyperesthesia, dysesthesia, simultaneous hot and cold sensations, tickling sensations, dysarthria, yawning, reduced appetite, hunger, and dystonia.

Respiratory: Infrequent was dyspnea. Rare were influenza, diseases of the lower respiratory tract, and hiccoughs.

Dermatological: Infrequent were erythema, pruritus, and skin rashes and eruptions. Rare was skin tenderness.

Urogenital: Rare were dysuria, frequency, dysmenorrhea, and renal calculus.

Miscellaneous: Infrequent were miscellaneous laboratory abnormalities, including minor disturbances in liver function tests, "serotonin agonist effect," and hypersensitivity to various agents. Rare was fever.

Postmarketing Experience: Frequency and causality for sumatriptan are not established for many of the following reports which come from worldwide postmarketing experience: Episodes of Prinzmetal's angina, myocardial infarction, acute renal failure, seizure, CVA, dysphasia, subarachnoid hemorrhage, and arrhythmias (atrial fibrillation, ventricular fibrillation, and ventricular tachycardia).

DRUG ABUSE AND DEPENDENCE: The abuse potential of Imitrex™ Injection cannot be fully delineated in advance of extensive marketing experience. One clinical study enrolling 12 patients with a history of substance abuse failed to induce subjective behavior and/or physiologic response ordinarily associated with drugs that have an established potential for abuse.

CERENEX™
PHARMACEUTICALS
DIVISION OF GLAXO INC
Research Triangle Park, NC 27709

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Now lactose-free doesn't

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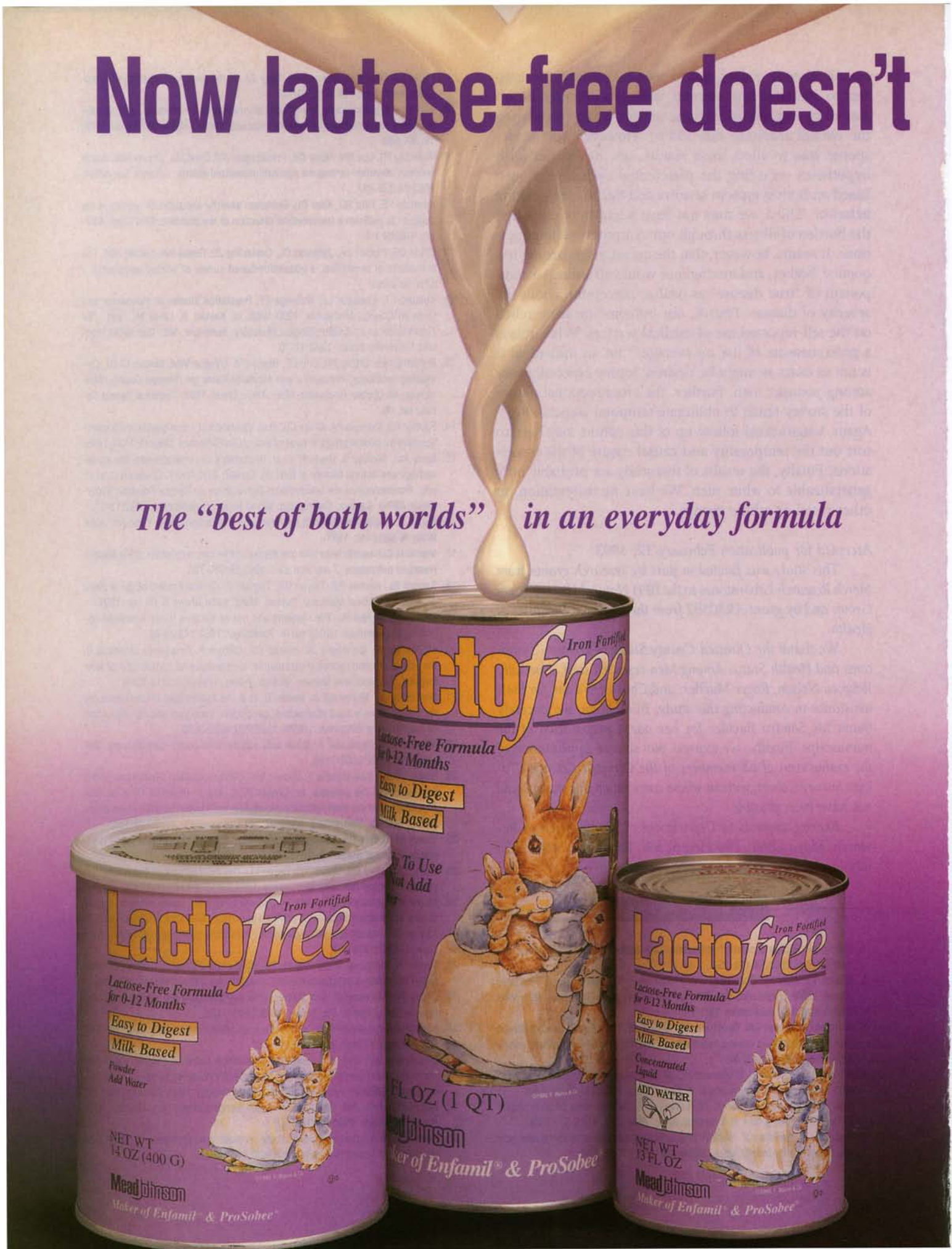

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The benefits of milk protein without the problems of lactose

- Keeps milk protein–the preferred† protein source–in the infant's diet
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Recommend...

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‡ We know of no studies showing clinical benefits from fatty acid profiles closer to breast milk, but Mead Johnson believes such profiles are prudent and appropriate.

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Effective with a low incidence of peptic ulcers

- As effective as NSAID standards for OA and RA[1]
- 0.5% incidence of peptic ulcers up to 1 year.*[1] Other G.I. symptoms comparable to other NSAIDs, including diarrhea, dyspepsia and abdominal pain
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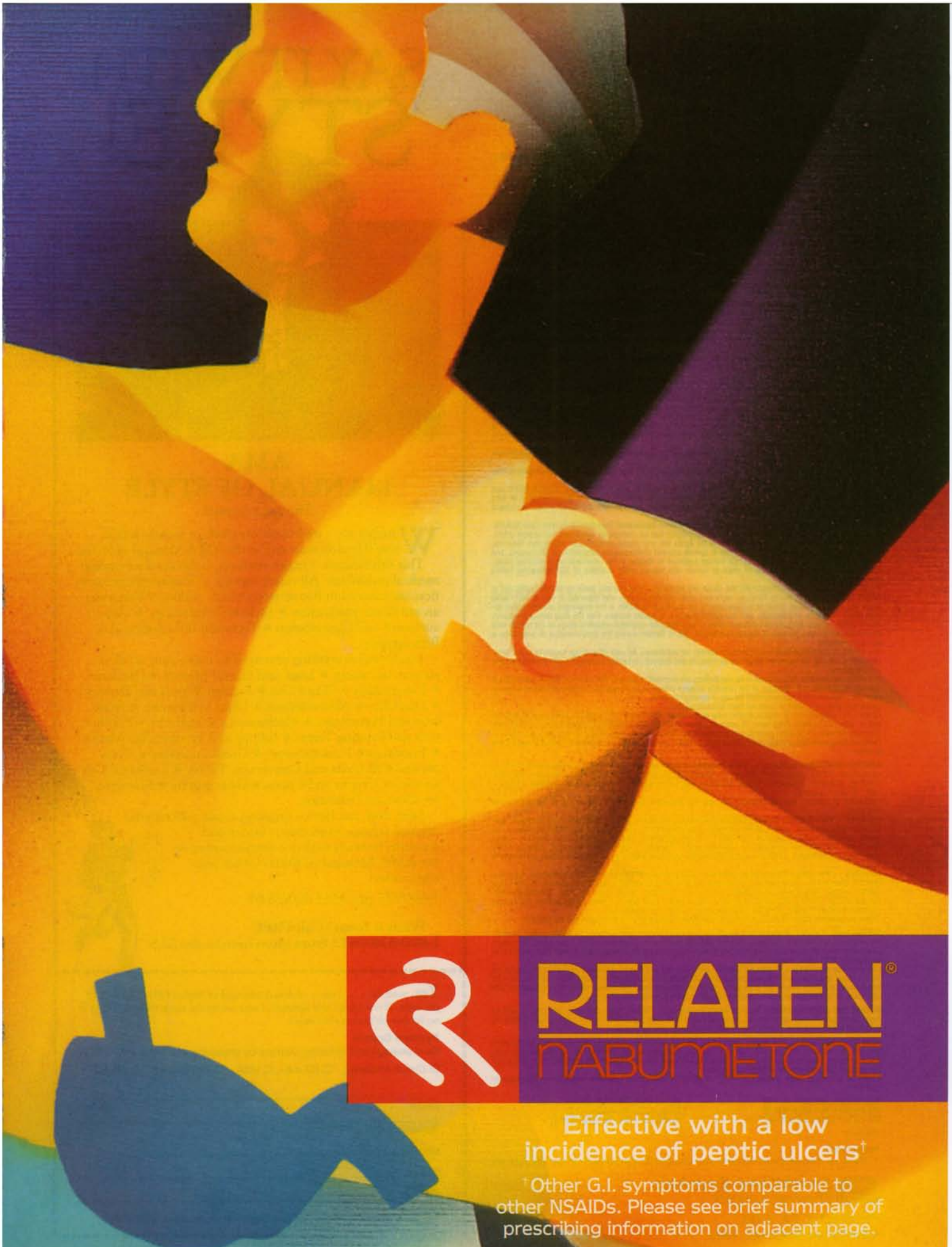
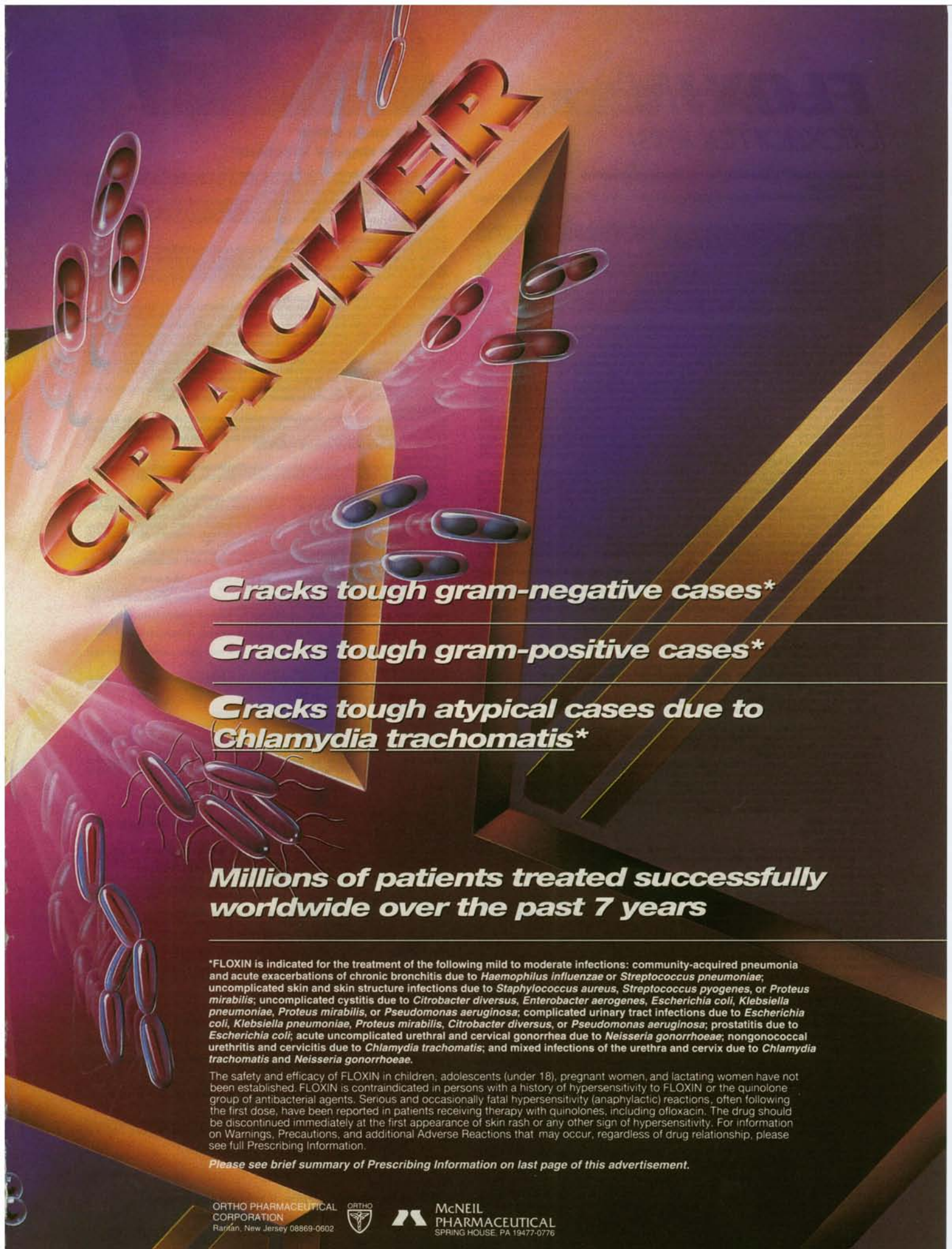
*Cumulative rate of ulcers by duration of treatment in U.S. clinical trials with *Relafen*. 1000 mg n=833, 1500 mg n=614, 2000 mg n=69; 95% confidence intervals (0.1%, 0.9%).


RELAFEN®
nabumetone
Effective with a low incidence of peptic ulcers†
†Other G.I. symptoms comparable to other NSAIDs. Please see brief summary of prescribing information on adjacent page.


FLOXIN® TABLETS
(ofloxacin tablets)
THE GRAM



Cracks tough gram-negative cases*

Cracks tough gram-positive cases*

Cracks tough atypical cases due to *Chlamydia trachomatis**

Millions of patients treated successfully worldwide over the past 7 years

***FLOXIN is indicated for the treatment of the following mild to moderate infections: community-acquired pneumonia and acute exacerbations of chronic bronchitis due to *Haemophilus influenzae* or *Streptococcus pneumoniae*; uncomplicated skin and skin structure infections due to *Staphylococcus aureus*, *Streptococcus pyogenes*, or *Proteus mirabilis*; uncomplicated cystitis due to *Citrobacter diversus*, *Enterobacter aerogenes*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, or *Pseudomonas aeruginosa*; complicated urinary tract infections due to *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Citrobacter diversus*, or *Pseudomonas aeruginosa*; prostatitis due to *Escherichia coli*; acute uncomplicated urethral and cervical gonorrhea due to *Neisseria gonorrhoeae*; nongonococcal urethritis and cervicitis due to *Chlamydia trachomatis*; and mixed infections of the urethra and cervix due to *Chlamydia trachomatis* and *Neisseria gonorrhoeae*.**

The safety and efficacy of FLOXIN in children, adolescents (under 18), pregnant women, and lactating women have not been established. FLOXIN is contraindicated in persons with a history of hypersensitivity to FLOXIN or the quinolone group of antibacterial agents. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, often following the first dose, have been reported in patients receiving therapy with quinolones, including ofloxacin. The drug should be discontinued immediately at the first appearance of skin rash or any other sign of hypersensitivity. For information on Warnings, Precautions, and additional Adverse Reactions that may occur, regardless of drug relationship, please see full Prescribing Information.

Please see brief summary of Prescribing Information on last page of this advertisement.

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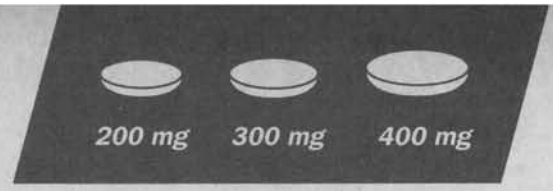
FLOXIN® TABLETS
(ofloxacin tablets)



Cracks tough cases in a wide range of infections*

BRIEF SUMMARY. CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

CONTRAINDICATIONS
Ofloxacin is contraindicated in persons with a history of hypersensitivity to ofloxacin or members of the quinolone group of antimicrobial agents.

WARNINGS
THE SAFETY AND EFFICACY OF OFLOXACIN IN CHILDREN, ADOLESCENTS (UNDER THE AGE OF 18 YEARS), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (SEE PEDIATRIC USE, USE IN PREGNANCY, AND NURSING MOTHERS SUBSECTIONS IN THE PRECAUTIONS SECTION.)

In the immature rat, the oral administration of ofloxacin at 5 to 16 times the recommended maximum human dose based on mg/kg or 1-3 times based on mg/m² increased the incidence and severity of osteochondrosis. The lesions did not regress after 13 weeks of drug withdrawal. Other quinolones also produce similar erosions in the weight-bearing joints and other signs of arthropathy in immature animals of various species. (See ***ANIMAL PHARMACOLOGY*** in full prescribing information.)

Ofloxacin has not been shown to be effective in the treatment of syphilis. Antimicrobial agents used in high doses for short periods of time to treat gonorrhea may mask or delay the symptoms of incubating syphilis. All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis. Patients treated with ofloxacin should have a follow-up serologic test for syphilis after three months.

Serious and occasionally fatal hypersensitivity (anaphylactic/anaphylactoid) reactions have been reported in patients receiving therapy with quinolones, including ofloxacin. These reactions often occur following the first dose. Some reactions were accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat or facial edema/swelling, etc.), airway obstruction (including bronchospasm, shortness of breath and acute respiratory distress), dyspnea, urticaria/hives, itching, and other serious skin reactions. A few patients had a history of hypersensitivity reactions. The drug should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated. (See ***PRECAUTIONS*** and ***ADVERSE REACTIONS.)***

Serious and sometimes fatal events of uncertain etiology have been reported in patients receiving therapy with quinolones including, extremely rarely, ofloxacin. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following: fever, rash or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson Syndrome, etc); vasculitis, arthralgia, myalgia, serum sickness; allergic pneumonitis; interstitial nephritis, acute renal insufficiency/failure; hepatitis, jaundice, acute hepatic necrosis/failure; anemia including hemolytic and aplastic, thrombocytopenia, including thrombotic thrombocytopenic purpura, leukopenia, agranulocytosis, pancytopenia, and/or other hematologic abnormalities. The drug should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity and supportive measures instituted. (See ***PRECAUTIONS: Information for Patients*** and ***ADVERSE REACTIONS***.)

Convulsions, increased intracranial pressure, and toxic psychosis have been reported in patients receiving quinolones, including ofloxacin. Quinolones, including ofloxacin, may also cause central nervous system stimulation which may lead to: tremors, restlessness/agitation, nervousness/anxiety, lightheadedness, confusion, hallucinations, paranoia and depression, nightmares, insomnia, and rarely suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving ofloxacin, the drug should be discontinued and appropriate measures instituted. As with all quinolones, ofloxacin should be used with caution in patients with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy, etc.) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction, etc.). (See ***PRECAUTIONS: General, DRUG INTERACTIONS*** and ***ADVERSE REACTIONS***.)

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ofloxacin, 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 any antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one 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 drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis. (See ***ADVERSE REACTIONS***.)

PRECAUTIONS
General:
Adequate hydration of patients receiving ofloxacin should be maintained to prevent the formation of a highly concentrated urine.

Administer ofloxacin with caution in the presence of renal or hepatic insufficiency/impairment. In patients with known or suspected renal or hepatic insufficiency/impairment, careful clinical observation and appropriate laboratory studies should be performed prior to and during therapy since elimination of ofloxacin may be reduced. In patients with impaired renal function (creatinine clearance < 50 mg/mL), alteration of the dosage regimen is necessary. (See ***CLINICAL PHARMACOLOGY*** and ***DOSAGE AND ADMINISTRATION*** in full prescribing information.)

Moderate to severe phototoxicity reactions have been observed in patients exposed to direct sunlight while receiving some drugs in this class, including ofloxacin. Excessive sunlight should be avoided. Therapy should be discontinued if phototoxicity (e.g., a skin eruption, etc.) occurs.

As with all quinolones, ofloxacin should be used with caution in any patient with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy, etc.) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction, etc.). (See: ***WARNINGS*** and ***DRUG INTERACTIONS***.)

As with other quinolones, disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glyburide/glibenclamide, etc.) or with insulin. In these patients careful monitoring of blood glucose is recommended. If a hypoglycemic reaction occurs in a patient being treated with ofloxacin, discontinue ofloxacin immediately and consult a physician. (See ***DRUG INTERACTIONS*** and ***ADVERSE REACTIONS.***)

As with any potent drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during prolonged therapy. (See ***WARNINGS*** and ***ADVERSE REACTIONS***.)

Information for Patients
Patients should be advised:
- to drink fluids liberally.
- that mineral supplements, vitamins with iron or minerals, calcium-, aluminum- or magnesium-based antacids or sucralfate should not be taken within the two-hour period before or within the two-hour period after taking ofloxacin. (See ***DRUG INTERACTIONS***.)
- that ofloxacin should not be taken with food.
- that ofloxacin may cause neurologic adverse effects (e.g., dizziness, lightheadedness, etc.) and that patients should know how they react to ofloxacin before they operate an automobile or machinery or engage in activities requiring mental alertness and coordination. (See ***WARNINGS*** and ***ADVERSE REACTIONS***.)
- that ofloxacin may be associated with hypersensitivity reactions, even following the first dose, to discontinue the drug at the first sign of a skin rash, hives or other skin reactions, a rapid heartbeat, difficulty in swallowing or breathing, any swelling suggesting angioedema (e.g., swelling of the lips, tongue, face; tightness of the throat, hoarseness, etc.), or any other symptom of an allergic reaction. (See ***WARNINGS*** and ***ADVERSE REACTIONS***.)
- to avoid excessive sunlight or artificial ultraviolet light while receiving ofloxacin and to discontinue therapy if phototoxicity (e.g., skin eruption, etc.) occurs.
- that if they are diabetic and are being treated with insulin or an oral hypoglycemic drug, to discontinue ofloxacin immediately if a hypoglycemic reaction occurs and consult a physician. (See ***PRECAUTIONS: General*** and ***DRUG INTERACTIONS.)***

Drug Interactions
Antacids, Sucralfate, Metal Cations, Multi-Vitamins: Quinolones form chelates with alkaline earth and transition metal cations. Administration of quinolones with antacids containing calcium, magnesium, or aluminum, with sucralfate, with divalent or trivalent cations such as iron, or with multivitamins containing zinc may substantially interfere with the absorption of quinolones resulting in systemic levels considerably lower than desired. These agents should not be taken within the two-hour period before or within the two-hour period after ofloxacin administration. (See ***DOSAGE AND ADMINISTRATION*** in full prescribing information.)
Caffeine: Interactions between ofloxacin and caffeine have not been detected.
Cimetidine: Cimetidine has demonstrated interference with the elimination of some quinolones. This interference has resulted in significant increases in half-life and AUC of some quinolones. The potential for interaction between ofloxacin and cimetidine has not been studied.
Cyclosporine: Elevated serum levels of cyclosporine have been reported with concomitant use of cyclosporine with some other quinolones. The potential for interaction between ofloxacin and cyclosporine has not been studied.
Drugs metabolized by Cytochrome P450 enzymes: Most quinolone antimicrobial drugs inhibit cytochrome P450 enzyme activity. This may result in a prolonged half-life for some drugs that are also metabolized by this system (e.g., cyclosporine, theophylline/methylxanthines, warfarin, etc.) when co-administered with quinolones. The extent of this inhibition varies among different quinolones. (See other ***DRUG INTERACTIONS.)***
Non-steroidal anti-inflammatory drugs: The concomitant administration of a non-steroidal anti-inflammatory drug, with a quinolone, including ofloxacin, may increase the risk of CNS stimulation and convulsive seizures. (See ***WARNINGS*** and ***PRECAUTIONS: General***.)
Probenecid: The concomitant use of probenecid with certain other quinolones has been reported to affect renal tubular secretion. The effect of probenecid on the elimination of ofloxacin has not been studied.
Theophylline: Although concurrent administration of some quinolones with theophylline may result in impaired elimination of theophylline, the extent of such impairment varies among different quinolones. Steady-state theophylline levels may increase when ofloxacin and theophylline are administered concurrently. In a pharmacokinetic study involving 15 healthy male subjects, steady-state peak theophylline concentration increased by an average of approximately 9%, and the AUC increased by an average of approximately 13% when oral ofloxacin and theophylline were administered concurrently. In clinical trials with intravenous ofloxacin, theophylline concentrations were determined in 41 patients who were treated with both drugs. In 38 patients, no apparent elevation in the serum theophylline was discernible. Marginal increases above the theophylline therapeutic range were reported in three patients; clinical toxicity was, however, not reported in these three patients. Generally, patients receiving theophylline in clinical trials of the intravenous formulation of ofloxacin reported nausea more frequently than those patients not receiving theophylline. As with some other quinolones, concomitant administration of ofloxacin may prolong the half-life of theophylline, elevate serum theophylline levels, and may increase the risk of theophylline-related adverse reactions. Theophylline levels should be closely monitored and theophylline dosage adjustments made if appropriate when ofloxacin is co-administered.
Warfarin: Some quinolones have been reported to enhance the effects of the oral anticoagulant warfarin or its derivatives. Therefore, if a quinolone antimicrobial is administered concomitantly with warfarin or its derivatives, the prothrombin time or other suitable coagulation test should be closely monitored.
Antidiabetic Agents (e.g., insulin, glyburide/glibenclamide, etc.): Since disturbances of blood glucose, including hyperglycemia and hypoglycemia, have been reported in patients treated concurrently with quinolones and an antidiabetic agent, careful monitoring of blood glucose is recommended when these agents are used concomitantly (See ***PRECAUTIONS: General*** and ***Information for Patients***.)

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Long-term studies to determine the carcinogenic potential of ofloxacin have not been conducted.

Ofloxacin was not mutagenic in the Ames bacterial test, *in vitro* and *in vivo* cytogenetic assay, sister chromatid exchange (Chinese Hamster and Human Cell Lines), unscheduled DNA Repair (UDS) using human fibroblasts, dominant lethal assays, or mouse micronucleus assay. Ofloxacin was positive in the UDS test using rat hepatocytes and Mouse Lymphoma Assay.

Pregnancy: Teratogenic Effects. Pregnancy Category C.
Ofloxacin has not been shown to have any teratogenic effects at oral doses as high as 810 mg/kg/day (11 times the recommended maximum human dose based on mg/m² or 50 times based on mg/kg) and 160 mg/kg/day (4 times the recommended maximum human dose based on mg/m² or 10 times based on mg/kg) when administered to pregnant rats and rabbits, respectively. Additional studies in rats with oral doses up to 360 mg/kg/day (5 times the recommended maximum human dose based on mg/m² or 23 times based on mg/kg) demonstrated no adverse effect on late fetal development, labor, delivery, lactation, neonatal viability, or growth of the newborn. Doses equivalent to 50 and 10 times the recommended maximum human dose of ofloxacin (based on mg/kg) were fetotoxic (i.e., decreased fetal body weight and increased fetal mortality) in rats and rabbits, respectively. Minor skeletal variations were reported in rats receiving doses of 810 mg/kg/day, which is more than 10 times higher than the recommended maximum human dose based on mg/m².

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

Nursing Mothers:
In lactating females, a single oral 200-mg dose of ofloxacin resulted in concentrations of ofloxacin in milk that were similar to those found in plasma. Because of the potential for serious adverse reactions from ofloxacin in nursing infants, 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. (See ***WARNINGS*** and ***ADVERSE REACTIONS.)***

Pediatric Use:
Safety and effectiveness in children and adolescents below the age of 18 years have not been established. Ofloxacin causes arthropathy (arthrosis) and osteochondrosis in juvenile animals of several species. (See ***WARNINGS***.)

ADVERSE REACTIONS
The following is a compilation of the data for ofloxacin based on clinical experience with both the oral and intravenous formulations. The incidence of drug-related adverse reactions in patients during Phase 2 and 3 clinical trials was 11%. Among patients receiving multiple-dose therapy, 4% discontinued ofloxacin due to adverse experiences.

In clinical trials, the following events were considered likely to be drug-related in patients receiving multiple doses of ofloxacin: nausea 3%, insomnia 3%, headache 1%, dizziness 1%, diarrhea 1%, vomiting 1%, rash 1%, pruritus 1%, external genital pruritus in women 1%, vaginitis 1%, dysgeusia 1%.

In clinical trials, the most frequently reported adverse events, regardless of relationship to drug, were: nausea 10%, headache 9%, insomnia 7%, external genital pruritus in women 6%, dizziness 5%, vaginitis 5%, diarrhea 4%, vomiting 4%.

In clinical trials, the following events, regardless of relationship to drug occurred in 1 to 3% of patients: Abdominal pain and cramps, chest pain, decreased appetite, dry mouth, dysgeusia, fatigue, flatulence, gastrointestinal distress, nervousness, pharyngitis, pruritus, fever, rash, sleep disorders, somnolence, trunk pain, vaginal discharge, visual disturbances, and constipation.

Additional events, occurring in clinical trials at a rate of less than 1%, regardless of relationship to drug, were:

Body as a whole:	asthenia, chills, malaise, extremity pain, pain, epistaxis
Cardiovascular System:	cardiac arrest, edema, hypertension, hypotension, palpitations, vasodilation
Gastrointestinal System:	dyspepsia
Genital/Reproductive System:	burning, irritation, pain and rash of the female genitalia; dysmenorrhea; menorrhagia; metrorrhagia
Musculoskeletal System:	arthralgia, myalgia
Nervous System:	seizures, anxiety, cognitive change, depression, dream abnormality, euphoria, hallucinations, paresthesia, syncope, vertigo, tremor, confusion
Nutritional/Metabolic:	thirst, weight loss
Respiratory System:	respiratory arrest, cough, rhinorrhea
Skin/Hypersensitivity:	angioedema, diaphoresis, urticaria, vasculitis
Special Senses:	decreased hearing acuity, tinnitus, photophobia
Urinary System:	dysuria, urinary frequency, urinary retention

The following laboratory abnormalities appeared in ≥ 1.0% of patients receiving multiple doses of ofloxacin. It is not known whether these abnormalities were caused by the drug or the underlying conditions being treated.

Hematopoietic:	anemia, leukopenia, leukocytosis, neutropenia, neutrophilia, increased band forms, lymphocytopenia, eosinophilia, lymphocytosis, thrombocytopenia, thrombocytosis, elevated ESR
Hepatic:	elevated: alkaline phosphatase, AST (SGOT), ALT (SGPT)
Serum chemistry:	hyperglycemia, hypoglycemia, elevated creatinine, elevated BUN
Urinary:	glucosuria, proteinuria, alkalinuria, hyposthenuria, hematuria, pyuria

Post-Marketing Adverse Events:
Additional adverse events, regardless of relationship to drug, reported from worldwide marketing experience with quinolones, including ofloxacin:

Clinical:

Cardiovascular System:	cerebral thrombosis, pulmonary edema, tachycardia, hypotension/shock, syncope
Endocrine/Metabolic:	hyper- or hypoglycemia, especially in diabetic patients on insulin or oral hypoglycemic agents (See ***PRECAUTIONS: General*** and ***DRUG INTERACTIONS***.)
Gastrointestinal System:	hepatic dysfunction including: hepatic necrosis, jaundice (cholestatic or hepatocellular), hepatitis; intestinal perforation; pseudomembranous colitis, GI hemorrhage; hiccough, painful oral mucosa, pyrosis (See ***WARNINGS).***
Genital/Reproductive System:	vaginal candidiasis
Hematopoietic:	anemia, including hemolytic and aplastic; hemorrhage, pancytopenia, agranulocytosis, leukopenia, reversible bone marrow depression, thrombocytopenia, thrombotic thrombocytopenic purpura, petechiae, ecchymosis/bruising (See ***WARNINGS***.)
Musculoskeletal:	tendinitis/rupture: weakness
Nervous System:	nightmares; suicidal thoughts or acts, disorientation, psychotic reactions, paranoia; phobia, agitation, restlessness, aggressiveness/hostility, manic reaction, emotional lability; peripheral neuropathy, ataxia, incoordination; possible exacerbation of: myasthenia gravis and extrapyramidal disorders; dysphasia, lightheadedness (See ***WARNINGS*** and ***PRECAUTIONS***.)
Respiratory System:	dyspnea, bronchospasm, allergic pneumonitis, stridor (See ***WARNINGS***.)
Skin/Hypersensitivity:	anaphylactic (-toid) reactions/shock; purpura, serum sickness, erythema multiforme/Stevens-Johnson syndrome, erythema nodosum, exfoliative dermatitis, hyperpigmentation, toxic epidermal necrolysis,conjunctivitis, photosensitivity, vesiculobullous eruption (See ***WARNINGS*** and ***PRECAUTIONS***.)
Special Senses:	diplopia, nystagmus, blurred vision, disturbances of: taste, smell, hearing and equilibrium, usually reversible following discontinuation
Urinary System:	anuria, polyuria, renal calculi, renal failure, interstitial nephritis, hematuria (See ***WARNINGS*** and ***PRECAUTIONS.***)

Laboratory:

Hematopoietic:	prolongation of prothrombin time
Serum chemistry:	acidosis, elevation of: serum triglycerides, serum cholesterol, serum potassium, liver function tests including: GGTP, LDH, bilirubin.
Urinary:	albuminuria, candiduria

In clinical trials using multiple-dose therapy, ophthalmologic abnormalities, including cataracts and multiple punctate lenticular opacities, have been noted in patients undergoing treatment with other quinolones. The relationship of the drugs to these events is not presently established.
CRYSTALLURIA and CYLINDRURIA HAVE BEEN REPORTED with other quinolones.

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

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**** Due to susceptible strains of indicated pathogens.***

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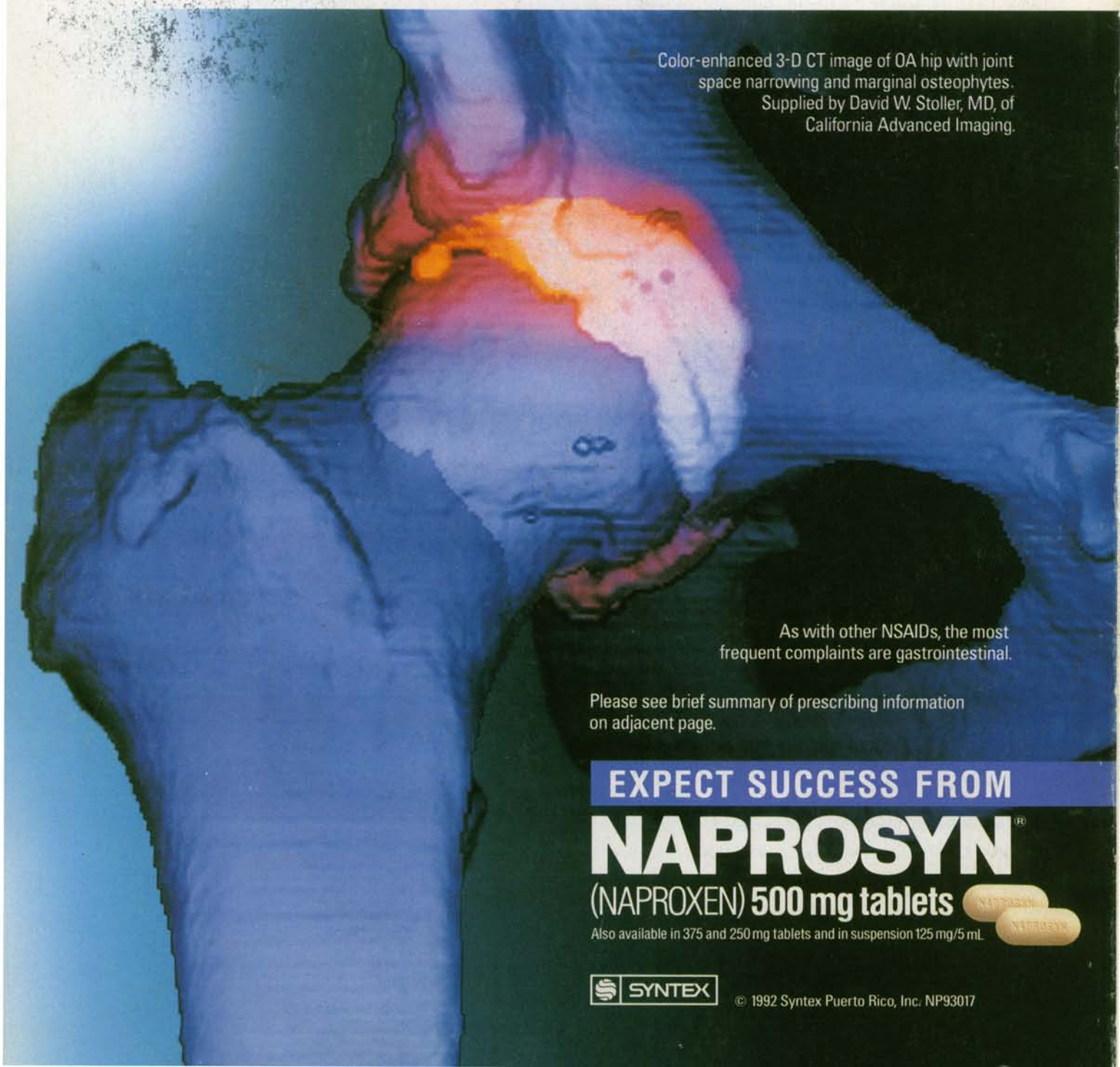

Color-enhanced 3-D CT image of OA hip with joint space narrowing and marginal osteophytes. Supplied by David W. Stoller, MD, of California Advanced Imaging.

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

Please see brief summary of prescribing information on adjacent page.

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