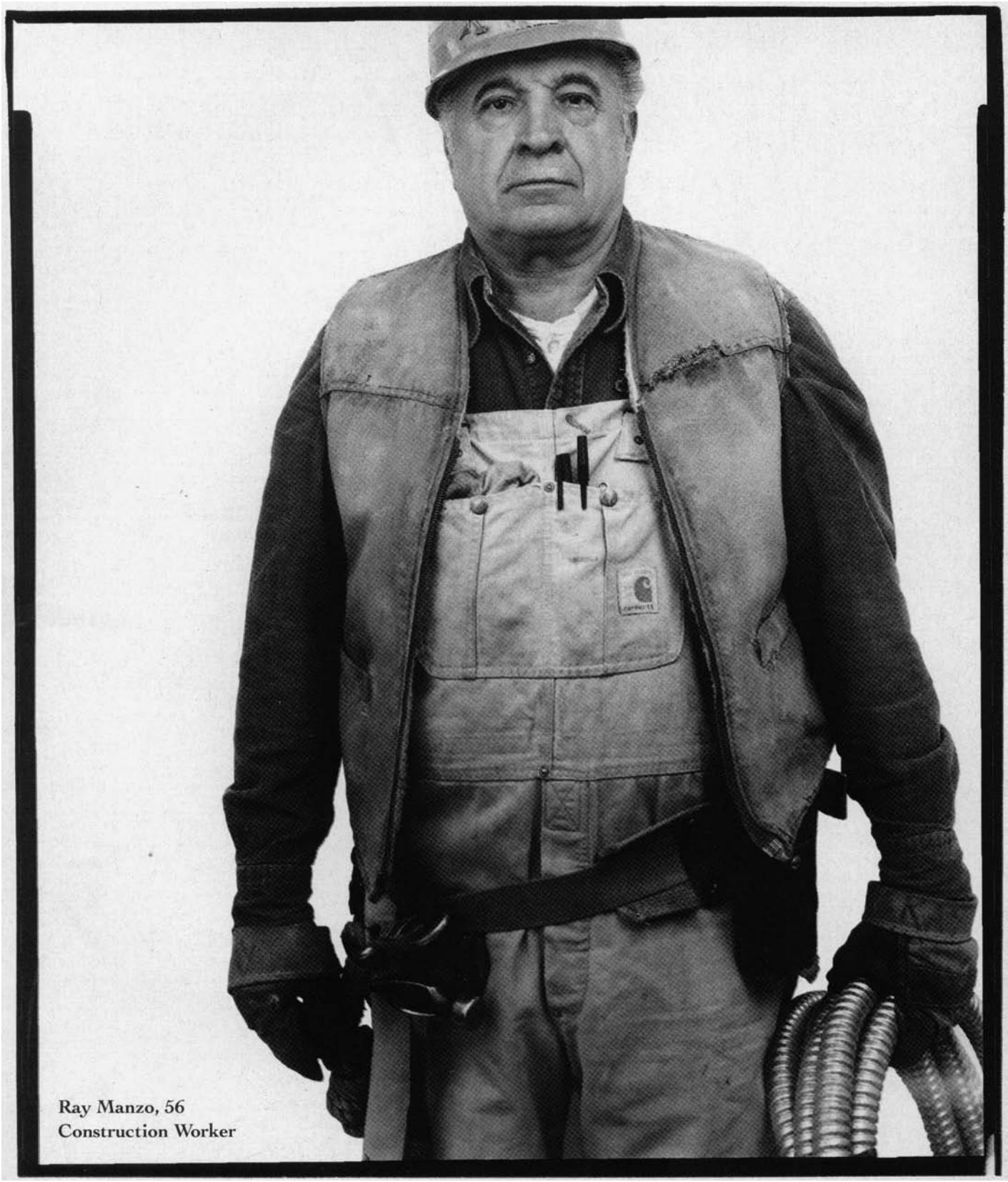


Ray Manzo, 56
Construction Worker

FOR TYPE II DIABETES,

TODAY'S LIFE DEMANDS INSULIN ON DEMAND

CAN'T ALWAYS EAT REGULARLY.

GLUCOTROL provides patients with insulin only when needed, responding on demand to meals and rising blood sugar[1]

DOUBLE SHIFTS.

GLUCOTROL, with insulin on demand, controls blood sugar quickly and effectively—all day and all night[1]

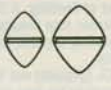
TOUGH PHYSICAL WORK.

GLUCOTROL works in response to meals; then insulin returns to near-normal levels once the meal challenge subsides[1,2]

When diet alone fails in NIDDM...

Glucotrol®

(glipizide) 5-mg and 10-mg Scored Tablets

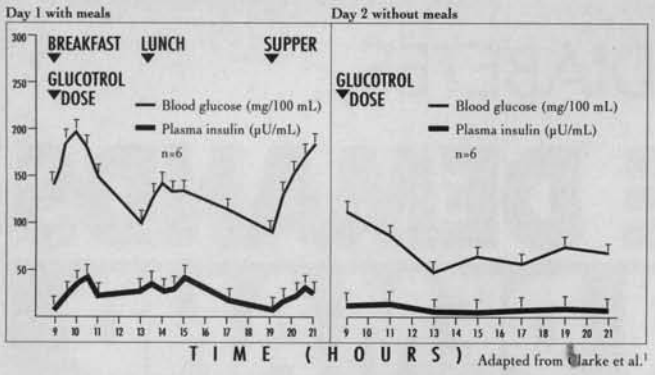


As with all sulfonylureas, hypoglycemia may occur.

Pfizer Pratt

Please see brief summary of prescribing information on last page.

INSULIN ON DEMAND RESPONDS TO MEALS— AND REMAINS AT BASAL LEVELS DURING FASTING



Adapted from Clarke et al.[1]

The effect of fasting on mean blood sugar and plasma insulin levels was measured in a 2-day study of six NIDDM patients whose blood sugar levels had been controlled by a single daily dose of 5 to 10 mg of GLUCOTROL. On the first day, patients were served three meals. On the second, they received no food. Each patient received their usual dose of GLUCOTROL at the start of each day.[1]

REFERENCES: 1. Clarke BF, Corrall RJM, Azzopardi J, Bhalla IP, Fraser DM, Duncan LJP. Clinical observations on glipizide: efficacy, duration of activity, and safety. In: *Glipizide: A Worldwide Review*. Princeton, NJ: Excerpta Medica; 1984:234-247. **2.** Goebel R, Leb G. Effects of glyburide and glipizide on levels of immunoreactive insulin and blood sugar. In: *Glipizide: A Worldwide Review*. Princeton, NJ: Excerpta Medica; 1984:9-15.

Brief Summary of Prescribing Information

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

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

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY: The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (*Diabetes*, 19, supp. 2:747-830, 1970).

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2½ times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of GLUCOTROL and of alternative modes of therapy. Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

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

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

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

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

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

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

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

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

RGCO28A93

FOR TYPE II DIABETES,

TODAY'S LIFE DEMANDS INSULIN ON DEMAND

When diet alone fails in NIDDM...

Glucotrol®

(glipizide) 5-mg and 10-mg Scored Tablets

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

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

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

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

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

Hypoglycemia: See PRECAUTIONS and OVERDOSAGE sections.

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

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

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

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

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

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

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

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

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

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

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

HOW SUPPLIED: GLUCOTROL tablets are white, dye-free, scored, diamond-shaped, and imprinted as follows:
5 mg—Pfizer 411; 10 mg—Pfizer 412.
5 mg Bottles: 100's (NDC 0049-4110-66); 500's (NDC 0049-4110-73); Unit Dose 100's (NDC 0049-4110-41)
10 mg Bottles: 100's (NDC 0049-4120-66); 500's (NDC 0049-4120-73); Unit Dose 100's (NDC 0049-4120-41)

CAUTION: Federal law prohibits dispensing without prescription.

More detailed professional information available on request.

Revised August 1990

Pfizer Pratt

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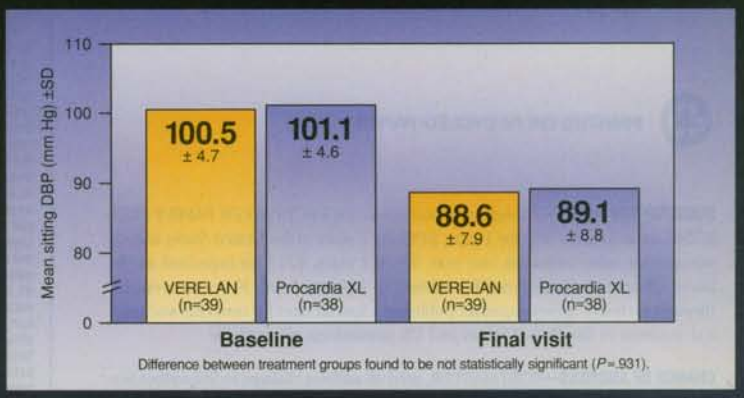
AMP

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

VERELAN

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

Reduction in mean DBP measured 24±2 hours after dosing



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

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

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

Please see brief summary of Prescribing Information on adjacent page.

ONCE-A-DAY

VERELAN®

Verapamil HCl 120 mg 180 mg 240 mg

PELLET-FILLED CAPSULES

ARCHIVES OF FAMILY MEDICINE

VOL 2 NO. 4, APR 1993

American Medical Association
Physicians dedicated to the health of America

TAGAMET® (brand of cimetidine)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Liquid: 300 mg/5 mL (400 mg/6.67 mL) in 8 fl oz (237 mL) amber glass bottles; 300 mg/5 mL and 400 mg/6.67 mL in single-dose units in packages of 10 (intended for institutional use only).

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

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

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

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

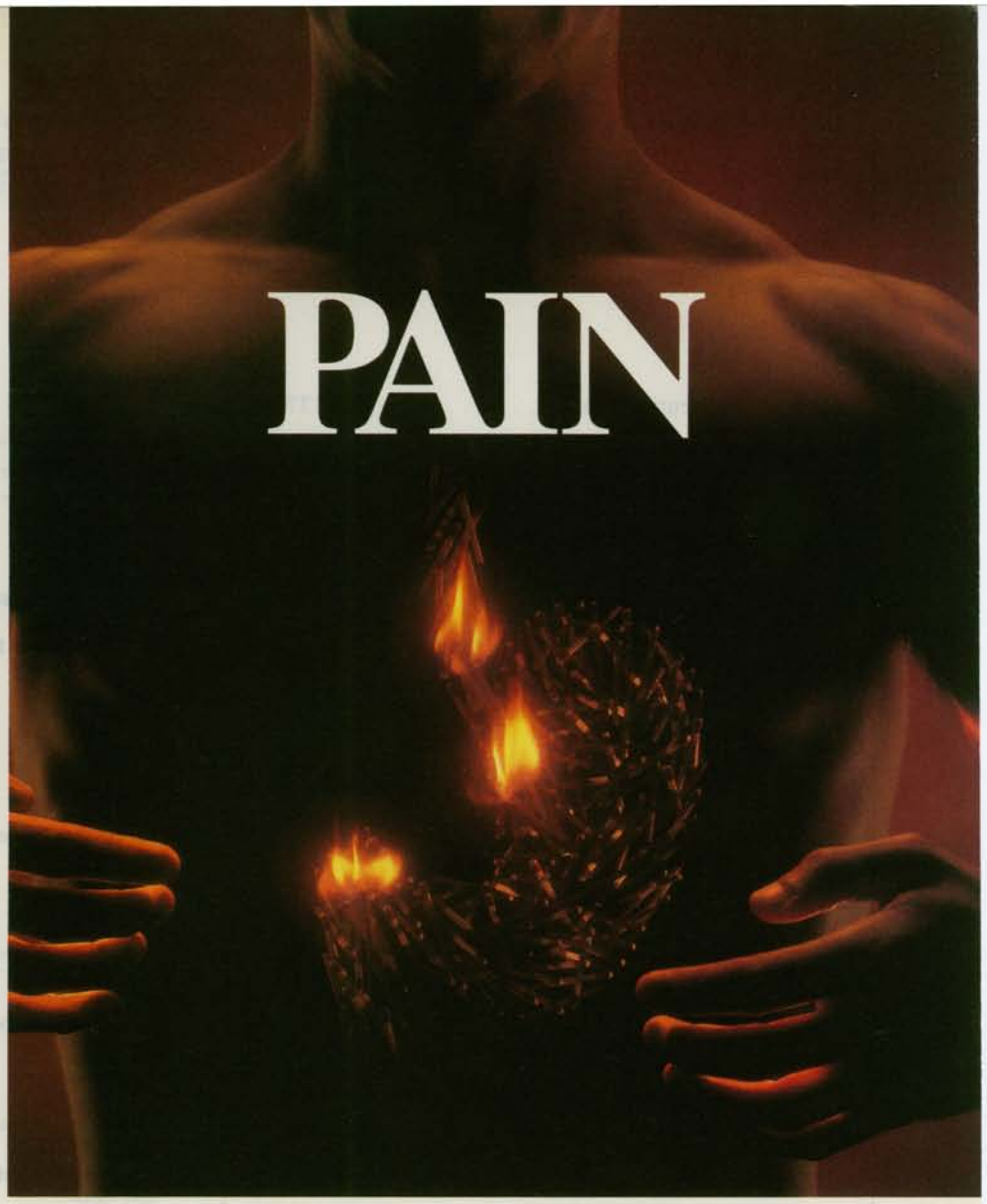
Tagamet (cimetidine hydrochloride) Injection premixed in single-dose plastic containers is manufactured for SmithKline Beecham Pharmaceuticals by Baxter Healthcare Corporation, Deerfield, IL 60015.

BRS-TG:L89

15 YEARS
BE RESPONSIBLE CARE

SB SmithKline Beecham Pharmaceuticals

Philadelphia, PA 19101



RELIEF

Tagamet® puts out the fire fast ...without burning a hole in your patient's pocket

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

Tagamet® cimetidine

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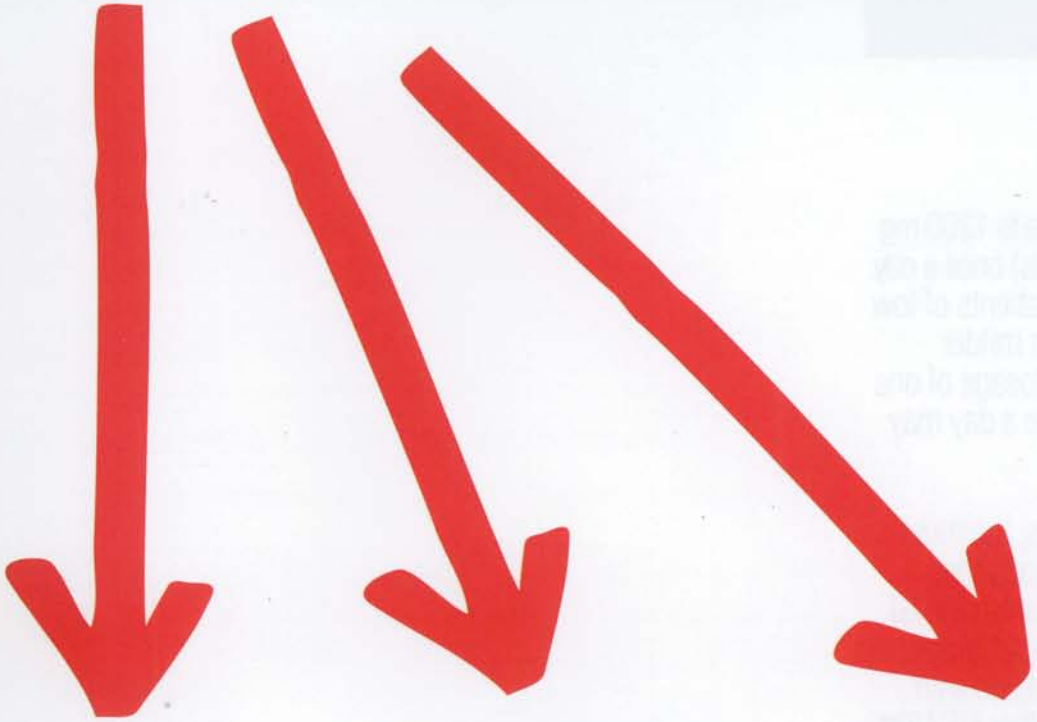
In osteoarthritis and rheumatoid arthritis

what you want in an NSAID*



☐ **Efficacy**

☐ **Tolerability**

☐ **Once-a-day dosing**

How to get it?

* Nonsteroidal anti-inflammatory drug.

Get

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

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

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

SEARLE

All you

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

DAYPRO™

(oxaprozin) 600-mg caplets

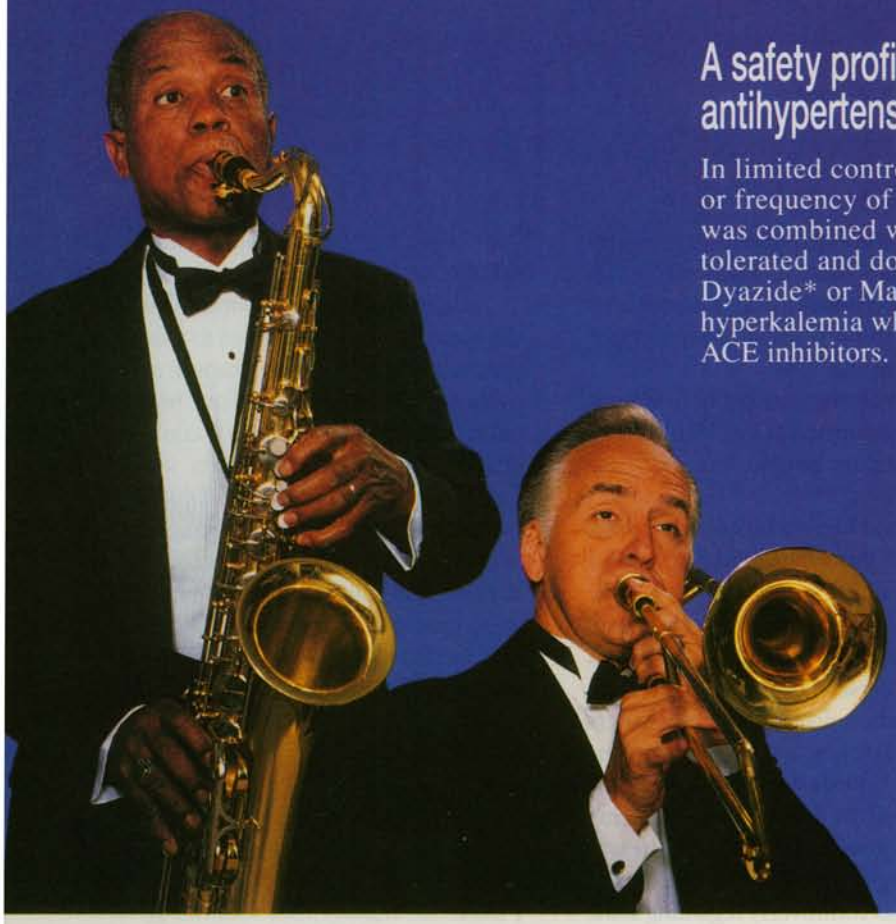
Efficacy
From the same chemical class as naproxen and ibuprofen, but with the extended duration of action of piroxicam[1]

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

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

want in an NSAID

IN CONCERT



A safety profile that works in concert with other antihypertensive agents

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

ONCE A DAY
LOZOL®
INDAPAMIDE 2.5mg TABLETS
PERFORMS WITH CONFIDENCE

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

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

Please see brief summary of prescribing information below.

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

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

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

WARNINGS: Infrequent cases of severe hyponatremia, accompanied by hypokalemia, have been reported with the use of recommended doses of indapamide primarily in elderly females. Symptoms were reversed by electrolyte replenishment (see PRECAUTIONS). Hypokalemia occurs commonly with diuretics (**see ADVERSE REACTIONS, hypokalemia**), and electrolyte monitoring is essential. In general, diuretics should not be given with lithium.

PRECAUTIONS: Perform serum electrolyte determinations at appropriate intervals, especially in patients who are vomiting excessively or receiving parenteral fluids, in patients subject to electrolyte imbalance, or in patients on a salt-restricted diet. In addition, patients should be observed for clinical signs of fluid or electrolyte imbalance, such as hyponatremia, hypochloremic alkalosis, or hypokalemia. The risk of hypokalemia secondary to diuresis and natriuresis is increased with larger doses, with brisk diuresis, with severe cirrhosis, and with concomitant use of corticosteroids or ACTH. Interference with adequate oral intake of electrolytes will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis, such as increased ventricular irritability.
Dilutional hyponatremia may occur in edematous patients; appropriate treatment is usually water restriction. In actual salt depletion, appropriate replacement is the treatment of choice. Chloride deficit is usually mild, not requiring specific treatment except in extraordinary circumstances (liver, renal disease).
Hyperuricemia may occur, and frank gout may be precipitated in certain patients receiving indapamide. Serum concentrations of uric acid should be monitored periodically.
Use with caution in patients with severe renal disease; consider withholding or discontinuing if progressive renal impairment is observed. Renal function tests should be performed periodically.
Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
Latent diabetes may become manifest and insulin requirements in diabetic patients may be altered during thiazide administration. Serum concentrations of glucose should be monitored routinely during treatment with indapamide.
Calcium excretion is decreased by diuretics pharmacologically related to indapamide. Serum concentrations of calcium increased only slightly with indapamide in long-term studies of hypertensive patients. Indapamide may decrease serum PBI levels without signs of thyroid disturbance. Complications of hyperparathyroidism have not been seen. Discontinue before tests of parathyroid function are performed.
Thiazides have exacerbated or activated systemic lupus erythematosus. Consider this possibility with indapamide.

DRUG INTERACTIONS: LOZOL may add to or potentiate the action of other antihypertensive drugs. The antihypertensive effect of the drug may be enhanced in the postsympathectomized patient. Indapamide may decrease arterial responsiveness to norepinephrine, but this does not preclude the use of norepinephrine.
In mouse and rat lifetime carcinogenicity studies, there were no significant differences in the incidence of tumors between the indapamide-treated animals and the control groups.

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

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

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.
Keep tightly closed. Store at room temperature. Avoid excessive heat.
Dispense in tight containers as defined in USP.
See product circular for full prescribing information. Revised: March 1992

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

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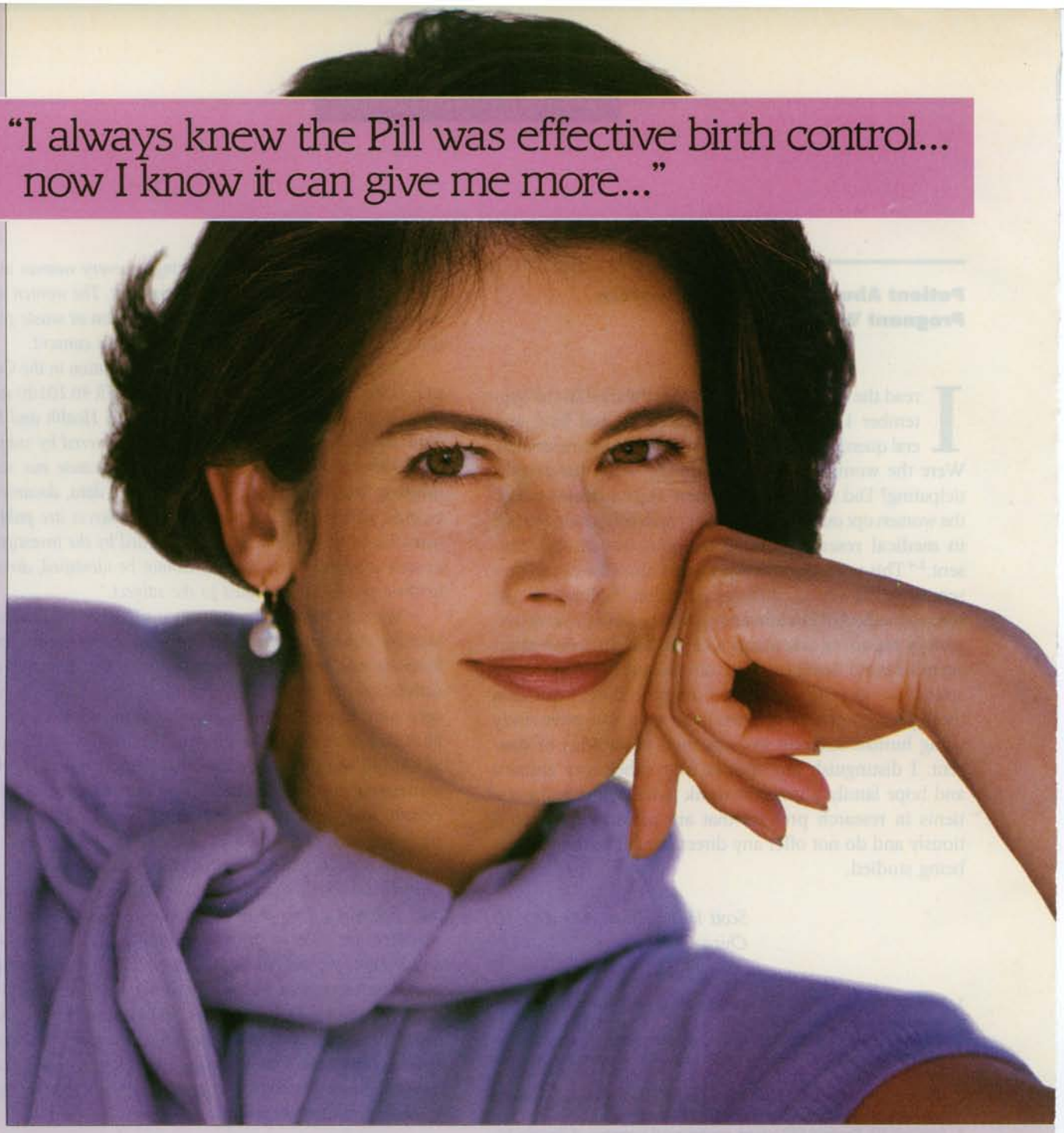
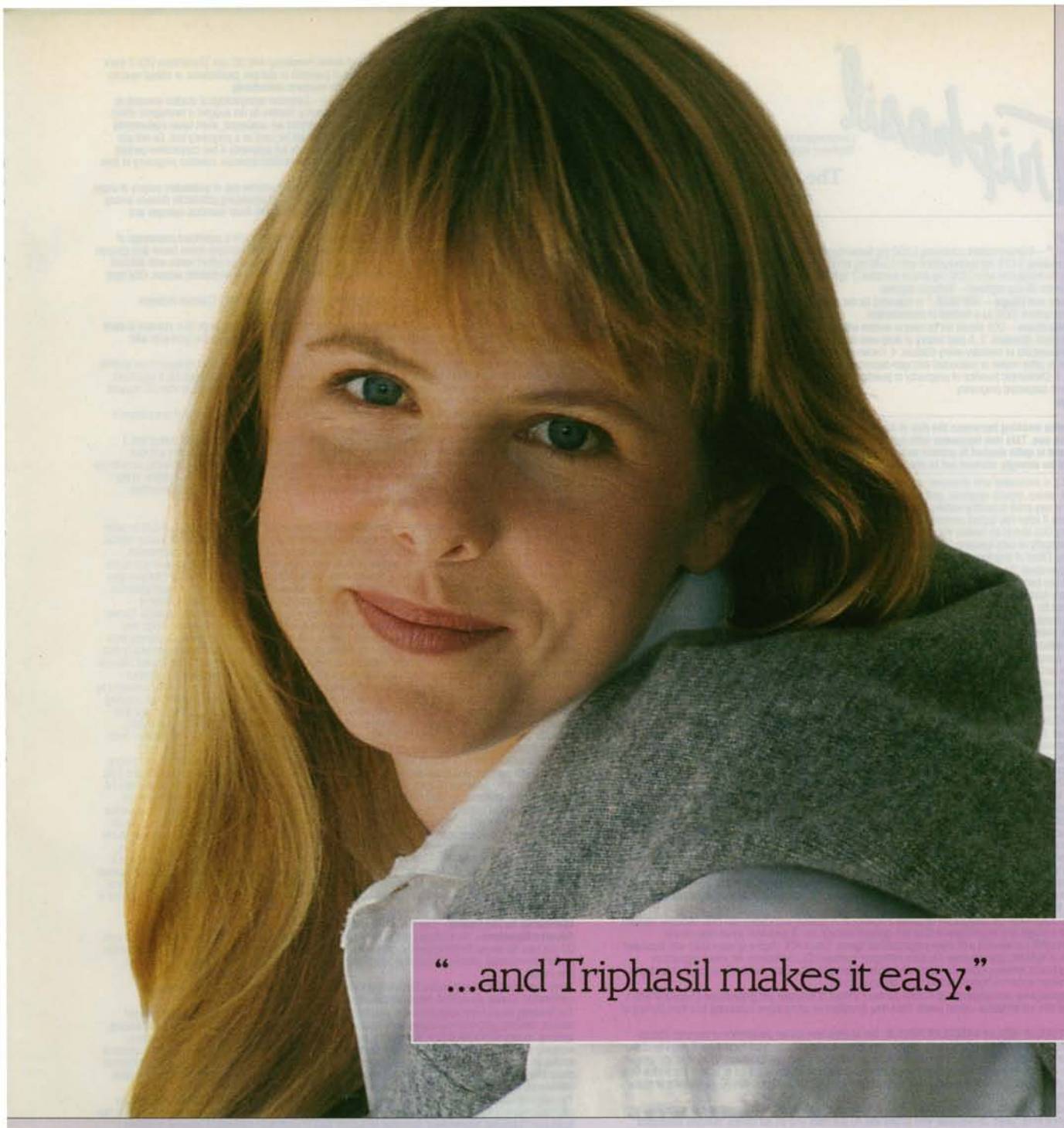
"I always knew the Pill was effective birth control... now I know it can give me more..."



Extra noncontraceptive health benefits for the days ahead.

In addition to reducing irregular menses and dysmenorrhea, all oral contraceptives have been shown to reduce the risks of pelvic inflammatory disease, ectopic pregnancy, benign breast disease, and ovarian cysts.[1-4] A 50% reduction in incidence of endometrial and ovarian cancer has also been shown – with protection extending at least 15 years after use.[5,6]*



"...and Triphasil makes it easy."

Patient acceptance day after day.

Triphasil offers flexible Day-1 or Sunday Start to help assure first-cycle compliance. Millions of cycles of experience demonstrate physician confidence.†

*These noncontraceptive health benefits related to the use of oral contraceptives are supported by epidemiological studies which largely utilized oral-contraceptive formulations containing doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg of mestranol.

†Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives.

Please see adjacent page for brief summary of prescribing information.

Triphasil®

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

The OC to start with and stay with.

Triphasil®

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

The OC to start with and stay with.

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

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

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

Warnings

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

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

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

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

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

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

A 2- to 4-fold increase in relative risk of postoperative thromboembolic complications has been reported with OCs. Relative risk of venous thrombosis in women with predisposing conditions is twice that of women without such conditions. If feasible, discontinue OCs at least 4 weeks prior to and for 2 weeks after elective surgery of a type associated with increased risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is associated with an increased thromboembolic risk, start OCs no earlier than 4 to 6 weeks after delivery in women not breast-feeding, or a mid-trimester pregnancy termination.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Precautions

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

Information for the Patient — See Patient Package Labeling.

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

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

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

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

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

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

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

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

References:

1. TRIPHASIL®-28 prescribing information, No. 3428-6. **2.** Rubin GL, Ory HW, Layde PM. *Am J Obstet Gynecol*.1982;144:630-635. **3.** Ory HW and the Women's Health Study. *Obstet Gynecol*.1981;57:137-144. **4.** Brinton LA, Vessey MP, Flavel R, et al. *Am J Epidemiol*.1981;113:203-214. **5.** The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development. *JAMA*.1987;257:796-800. **6.** The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development. *N Engl J Med*. 1987;316:650-655.

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

Results: In the 1006 patients, mortality was 18.7% among those randomized to nifedipine and 15.6% in the patients randomized to placebo. This reflected an increased mortality of 7.8% as compared with 5.5% during the first 6 days in the nifedipine and placebo groups, respectively (adjusted mortality odds ratio by logistic regression, 1.60; 95% confidence interval, 0.86 to 3.00). Among the 826 patients who continued treatment, mortality was equal in the nifedipine (9.3%) and placebo (9.5%) groups. No differences in the rates of nonfatal MI (5.1% and 4.2% in the nifedipine and placebo groups, respectively), hospitalization due to unstable angina, and frequency of chest pain reported during follow-up were observed. An increased rate of sudden death (4.9%) in the placebo group in comparison with the nifedipine group (2.3%) was not statistically significant on post hoc testing, nor was an effect of nifedipine demonstrable in post hoc analyses by congestive heart failure status of randomized patients.
Conclusions: Nifedipine as a prophylactic treatment in patients immediately after acute MI or in survivors recovering 1 week or longer after acute MI appears ineffective. Early routine administration of nifedipine in acute MI, other than to patients in whom it may be specifically indicated (eg, those with Prinzmetal's variant angina or severe hypertension) may be hazardous and seems to be contraindicated.

(1993;153:345-353) Uri Goldbourt et al. Reprint requests to Dr Elieser Kaplinsky, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, 52621 Israel.

ARCHIVES OF GENERAL PSYCHIATRY

Maintenance Drug Treatment of Panic Disorder: I. Results of a Prospective, Placebo-Controlled Comparison of Alprazolam and Imipramine

One hundred six patients diagnosed according to *DSM-III* as suffering from agoraphobia with panic disorder, panic disorder with limited phobic avoidance, or uncomplicated panic disorder entered an acute 8-week treatment phase. Patients who improved received an additional 6 months' maintenance treatment. Significantly more patients treated with alprazolam than with imipramine hydrochloride or placebo remained in therapy and experienced panic attack and phobia relief during the acute treatment phase. During the maintenance phase, neither tolerance nor daily dose increase was observed. All patients who completed the maintenance

Strong Relief Whenever You Need It

- ❑ Flexible dosing provides consistent pain relief
- ❑ Maximum dose 1,200 mg/day
- ❑ Effective maintenance dose as little as 600 mg/day
- ❑ Rapid onset of action...30 minutes[1]
- ❑ Favorable safety profile in younger *and* older adult patients[1]*...

☑ GI† ☑ Renal‡ ☑ Hepatic‡

FIRST-LINE THERAPY FOR PAIN AND OSTEOARTHRITIS

LODINE®
200 mg/300 mg CAPSULES ETODOLAC

Strong on pain, easy to live with

*Safety in children has not been established. In patients 65 years and older, no substantial differences in the pharmacokinetics or side-effects profile of LODINE were seen compared with the general population.

†As with other NSAIDs, the most frequent complaints relate to the GI tract. In patients treated chronically with NSAID therapy, serious GI toxicity such as perforation, ulceration, and bleeding can occur.

‡As with other NSAIDs, rare renal and hepatic reactions have been reported. Please see "Precautions" section of prescribing information.

Please see next page for brief summary of prescribing information.

STRONG ON PAIN, EASY TO LIVE WITH

LODINE®
200 mg/300 mg CAPSULES ETODOLAC

LODINE® (etodolac) Capsules
BRIEF SUMMARY OF PRESCRIBING INFORMATION.
SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

INDICATIONS AND USAGE: Lodine (etodolac) is indicated for acute and long-term use in the management of signs and symptoms of osteoarthritis. Lodine is also indicated for the management of pain.

CONTRAINDICATIONS: Hypersensitivity to Lodine. Do not give if Lodine, aspirin, or other NSAIDs have induced asthma, rhinitis, urticaria, or other allergic reactions since fatal asthmatic reactions have been reported in such patients.

WARNINGS: RISK OF GASTROINTESTINAL (GI) ULCERATION, BLEEDING, AND PERFORATION WITH NSAID THERAPY: Serious GI toxicity (e.g., bleeding, ulceration, perforation) can occur at any time, with or without warning symptoms, during chronic therapy. Minor upper GI problems are common early in therapy but physicians should remain alert for ulceration and bleeding even without previous GI-tract symptoms. Occurrence of serious GI toxicity is about 1% after 3 to 6 months of therapy; 2% to 4% after 1 year. Patients should be informed of signs and symptoms of serious GI toxicity and what to do if they occur. Studies have failed to identify a patient subset not at risk for peptic ulceration and bleeding. Prior history of serious GI events and other risk factors of peptic ulcer disease (e.g., alcoholism, smoking, etc.) are associated with increased risk. Elderly or debilitated patients tolerate ulceration or bleeding less well and have more fatal GI events. High doses probably carry a greater risk. Consider benefit versus risk (of GI toxicity) in prescribing higher recommended doses. **PRECAUTIONS: Renal Effects:** Like other NSAIDs, long-term administration of etodolac to rats has resulted in renal papillary necrosis and other renal medullary changes. Renal pelvic transitional epithelial hyperplasia, a spontaneous change occurring with variable frequency, was observed with increased frequency in treated male rats in a 2-year chronic study. The cause-effect relationship to etodolac has not been established. A second form of renal toxicity is seen in patients with conditions in which renal prostaglandins support the maintenance of renal perfusion. In these patients, NSAIDs may cause a dose-dependent reduction in prostaglandin formation and renal blood flow which may precipitate overt renal failure. Patients with impaired renal or hepatic function, heart failure, those on diuretics, and the elderly are at greatest risk. Discontinuation of NSAIDs is usually followed by recovery. Etodolac metabolites are eliminated primarily by the kidneys. The extent of inactive glucuronide metabolite accumulation in renal failure patients has not been studied. As with other drugs whose metabolites are excreted by the kidney, the possibility that adverse reactions (not listed in **ADVERSE REACTIONS**) may be attributable to these metabolites should be considered. **Hepatic Effects:** Borderline elevations of liver tests may occur in up to 15% and may disappear, remain unchanged, or progress with continued therapy. Patients with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated further as serious hepatic reactions have been reported. Such reactions are rare, but Lodine should be discontinued if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.). **Hematological Effects:** Anemia, which may be due to fluid retention, GI blood loss, or an effect upon erythropoiesis, is sometimes seen in patients receiving NSAIDs. Hemoglobin or hematocrit should be checked if signs or symptoms of anemia develop. Drugs which inhibit prostaglandin biosynthesis may interfere with platelet function and vascular responses to bleeding. Carefully observe patients on Lodine who may be adversely affected by such actions. **Fluid Retention and Edema:** Fluid retention and edema have been observed in some patients; therefore, use with caution in those with fluid retention, hypertension, or heart failure. **Information for Patients:** Physicians should discuss potential risks (see **WARNINGS, PRECAUTIONS, ADVERSE REACTIONS**) and likely benefits with patients, especially when other drugs offer an acceptable alternative for less serious conditions. **Laboratory Tests:** Serious GI-tract ulceration and bleeding can occur without warning symptoms; observe chronically treated patients for signs/symptoms of ulceration and bleeding and inform them of the importance of this follow-up. **Drug Interactions: Antacids:** Concomitant antacid administration has no apparent effect on the extent of Lodine (etodolac) absorption or its time-to-peak. However, antacids can decrease the peak concentration reached by 15-20%. **Aspirin:** Concomitant aspirin administration is not generally recommended because of the potential for increased adverse effects. **Warfarin:** Given concomitantly with Lodine results in reduced protein binding of warfarin, but no change in free warfarin clearance. There is no significant difference in the pharmacodynamic effect of warfarin administered alone or with Lodine as measured by prothrombin time. Concomitant therapy should not require dosage adjustment of either drug; however, exercise caution because interactions have been seen with other NSAIDs. **Diuretics:** Lodine has no apparent pharmacokinetic interaction when administered with furosemide or hydrochlorothiazide; nor does Lodine attenuate the diuretic response of either drug in normal volunteers. Use with caution in patients receiving diuretics who have cardiac, renal or hepatic failure (see Renal Effects). **Cyclosporine, Digoxin, Lithium, Methotrexate:** Through effects on renal prostaglandins, Lodine (etodolac) may cause changes in elimination of these drugs leading to elevated serum levels of digoxin, lithium, and methotrexate and increased toxicity. Cyclosporine-associated nephrotoxicity may also be enhanced. **Protein Binding:** *In vitro* studies show that the etodolac free fraction is not significantly altered by acetaminophen, ibuprofen, indomethacin, naproxen, piroxicam, chlorpropamide, glipizide, glyburide, phenytoin, and probenecid. However, phenylbutazone causes it to increase (by about 80%). Despite lack of *in vivo* data regarding phenylbutazone's effect on etodolac clearance, phenylbutazone coadministration is not recommended. **Drug/Laboratory Test Interactions:** A false positive reaction for urinary bilirubin (urobilin) may occur due to the presence of phenolic metabolites of etodolac. Diagnostic dip-stick methodology to detect urinary ketone bodies has occasionally resulted in false positive findings. Generally, this is not associated with other clinically significant events; no dose-relationship has been observed. Lodine therapy is associated with a small decrease in serum uric acid levels. In clinical trials, mean decreases of 1-2 mg/dL were observed in arthritic patients after 4 weeks of etodolac (600 mg to 1000 mg/day). Levels then remained stable for up to one year of therapy. **Carcinogenesis, Mutagenesis, and Impairment of Fertility:** No carcinogenic effect was observed in mice or rats at doses studied. Etodolac was not mutagenic in *in vitro* or *in vivo* animal studies; however, some, but not all, human *in vitro* data showed some chromatid abnormalities. No impairment of fertility in rats was seen with oral doses up to 16 mg/kg, however, reduced implantation of fertilized eggs occurred in the 8 mg/kg group. **(See Package Insert for details) Teratogenic Effects:** Pregnancy Category C: In teratology studies, isolated occurrences of limb development alterations were found, including polydactyly, oligodactyly, syndactyly, and unossified phalanges in rats and oligodactyly and synostosis of metatarsals in rabbits. The frequency and dosage group distribution of these findings did not establish a clear drug or dose-response relationship. Use not recommended in pregnancy. **Labor and Delivery, Nursing Mothers, Pediatric Use:** Safety has not been established in these patients, therefore its use is not recommended. **Geriatric Population:** Because of Lodine's pharmacokinetic and side effect profiles, no dosage adjustment is generally necessary in the elderly. Exercise caution, however, when increasing the dose because the elderly seem to tolerate NSAID side effects less well than younger patients. (See Pharmacokinetics in Package Insert) **ADVERSE REACTIONS:** Information was derived from 2,629 arthritic patients on Lodine in double-blind and open-label clinical trials lasting 4 to 320 weeks and worldwide post-marketing surveillance studies in about 60,000 patients. Most adverse reactions were mild and transient; 9% discontinued therapy due to adverse events. New patient complaints (with incidence ≥ 1%) are listed below by body system. Incidences were determined from clinical trials involving 465 patients with osteoarthritis on 300 to 500 mg of Lodine (etodolac) BID (i.e., 600 to 1000 mg per day). **Incidence ≥ 1% - Probably Causally Related: Body as a whole:** Chills and fever. **Digestive system:** Dyspepsia (10%), abdominal pain[†], diarrhea[†], flatulence[†], nausea[†], constipation, gastritis, melena, vomiting. **Nervous system:** Asthenia/malaise[†], dizziness[†], depression, nervousness. **Skin and appendages:** Pruritus, rash. **Special senses:** Blurred vision, tinnitus. **Urogenital system:** Dysuria, urinary frequency. [†]Drug-related patient complaints occurring in 3-9% of patients treated with Lodine. Drug-related patient complaints occurring in fewer than 3%, but more than 1%, are unmarked. **Incidence < 1% - Probably Causally Related** (Adverse reactions reported only in worldwide postmarketing experience, not seen in clinical trials, are considered rarer and are italicized): **Cardiovascular system:** Hypertension, congestive heart failure, flushing, palpitations, syncope. **Digestive system:** Thirst, dry mouth, ulcerative stomatitis, anorexia, eructation, elevated liver enzymes, hepatitis, *jaundice*, PUB, i.e., peptic ulcer with or without bleeding and/or perforation. **Hemic and lymphatic system:** Ecchymosis, anemia, thrombocytopenia, bleeding time increased. **Metabolic and nutritional:** Edema, serum creatinine increase. **Nervous system:** Insomnia, somnolence. **Respiratory system:** Asthma. **Skin and appendages:** Angioedema, sweating, urticaria, vesiculobullous rash, *cutaneous vasculitis with purpura, Stevens-Johnson Syndrome*, hyperpigmentation. **Special senses**: Photophobia, transient visual disturbances. **Incidence < 1% - Causal Relationship Unknown** [Medical events occurring under circumstances where causal relationship to Lodine (etodolac) is uncertain. These reactions are listed as alerting information for physicians]: **Body as a whole:** Infection. **Cardiovascular system:** Arrhythmias, myocardial infarction. **Digestive system:** Esophagitis with or without stricture or cardiospasm, colitis. **Hemic and lymphatic system:** Leukopenia. **Metabolic and nutritional:** Change in weight. **Nervous System:** Paresthesia, confusion. **Respiratory System:** Bronchitis, dyspnea, pharyngitis, rhinitis, sinusitis. **Skin and Appendages:** Maculopapular rash, alopecia, skin peeling, photosensitivity. **Special Senses:** Conjunctivitis, deafness, taste perversion. **Urogenital System:** Cystitis, hematuria, leukorrhea, renal calculus, interstitial nephritis, uterine bleeding irregularities. **DRUG ABUSE AND DEPENDENCE:** Lodine is a non-narcotic drug; animal studies indicate that it has no addiction potential in humans. **OVERDOSAGE:** Symptoms of acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain which are generally reversible with supportive care. GI bleeding and coma have occurred following massive ibuprofen or mefenamic acid overdose. Hypertension, acute renal failure, and respiratory depression are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs and may occur following overdose. Management is symptomatic and supportive; there are no specific antidotes. Gut decontamination, via emesis and/or activated charcoal with an osmotic cathartic, may be indicated in symptomatic patients seen within 4 hours or following a large overdose. Forced diuresis, alkalinization of the urine, hemodialysis or hemoperfusion would probably not be useful due to etodolac's high protein binding. **DOSAGE AND ADMINISTRATION: Analgesia:** For acute pain, 200 to 400 mg every 6-8 hours, as needed, not to exceed a total daily dose of 1200 mg. Total daily dose should not exceed 20 mg/kg in patients weighing 60 kg or less. **Osteoarthritis:** Initially 800-1200 mg/day in divided doses, followed by dosage adjustment within the range of 600 to 1200 mg/day given in divided doses: 400 mg TID or BID; 300 mg QID, TID, or BID; 200 mg QID or TID. Total daily dose should not exceed 1200 mg. For patients weighing 60 kg or less, total daily dose should not exceed 20 mg/kg. **HOW SUPPLIED:** 200 and 300 mg capsules. Protect from moisture.

3/20/91 4000-2

"It works for me!"

- ❑ **Rapid onset of action —30 minutes[1]**
- ❑ **Effective relief of pain and inflammation[1]**
- ❑ **Up to 1,200 mg per day: —convenient maintenance dosing for chronic pain**
  —q 6 to 8 hours prn for acute pain
- ❑ **As well-tolerated in older as in younger adult patients[1]***

*Safety in children has not been established. In patients 65 years and older, no substantial differences in the pharmacokinetics or side-effects profile of LODINE were seen compared with the general population.

Reference: 1. Data on file, Wyeth-Ayerst Laboratories; LODINE® Prescribing Information.

63533

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A·H·ROBINS

"Specify Dispense As Written"

In Mild Hypertension[1]

Dependable Control Is Shaped Like This

Effective in mild hypertension[1*†]

Excellent safety profile[1]

Potassium and magnesium conservation[1,2]

Prescribe the Shape to Remember

Once-a-day **MAXZIDE®-25 MG**

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

* Normalization of diastolic BP (<90 mmHG) in 79% of mildly hypertensive patients within 4 weeks.

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

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

Please see adjacent page for Brief Summary, including **WARNINGS**, **CONTRAINDICATIONS**, and **ADVERSE REACTIONS**.

Specify

"Dispense As Written"

Prescribe the Shape to Remember

Once-a-day MAXZIDE®-25 MG

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

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

Brief Summary

Please see package insert for full prescribing information.

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

WARNINGS

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

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

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

PRECAUTIONS

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

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

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

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

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

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

Insulin requirements in diabetic patients may be changed. Thiazides may cause manifestation of latent diabetes mellitus. Sensitivity reactions to thiazides may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus by thiazides has been reported.

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

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

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

MAXZIDE may interfere with quinidine measurement.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies have not been performed to evaluate the mutagenic or carcinogenic potential of MAXZIDE.

Hydrochlorothiazide: Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately

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

600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic in *in vitro* assays using strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 of *Salmonella typhimurium* (Ames assay) and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or in *in vivo* assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 μg/mL, and in the *Aspergillus nidulans* nondisjunction assay at an unspecified concentration.

In rat and mice studies, hydrochlorothiazide, given in the diet in doses up to 100 mg/kg and 4 mg/kg prior to conception and during gestation, had no adverse effects on the fertility of either sex.

Triamterene: Studies have not been performed to determine the carcinogenic or mutagenic potential of triamterene. Reproductive studies have been performed in rats at doses up to 30 times the human dose and have revealed no evidence of impaired fertility.

Pregnancy Category C: Teratogenic Effects–Animal reproduction studies have not been conducted with MAXZIDE. It is also not known if MAXZIDE can cause fetal harm when administered to a pregnant woman.

Hydrochlorothiazide: Studies in which hydrochlorothiazide was orally administered to pregnant mice and rats during their respective periods of major organogenesis at doses up to 3000 mg and 1000 mg hydrochlorothiazide/kg, respectively, provided no evidence of harm to the fetus. There are, however, no adequate and well-controlled studies in pregnant women.

Triamterene: Reproduction studies performed in rats at doses up to 30 times the human dose have revealed no evidence of impaired fertility or harm to the fetus due to triamterene. There are no adequate and well-controlled studies in pregnant women.

Because animal reproduction studies are not always predictive of human response, MAXZIDE should be used during pregnancy only if clearly needed.

Nonteratogenic Effects: Thiazides and triamterene cross the placental barrier and appear in cord blood of animals. Anticipated benefit of the use of MAXZIDE should be weighed against possible hazards to the fetus, including fetal or neonatal jaundice, thrombocytopenia following thiazides, and possible other adverse reactions that have occurred in the adults.

Nursing Mothers: Thiazides appear and triamterene may appear in breast milk. If use is essential, the patient should stop nursing.

Pediatric Use: The safety and effectiveness of MAXZIDE in children have not been established.

ADVERSE REACTIONS

Side effects observed in association with the use of MAXZIDE, other combination products containing triamterene/hydrochlorothiazide, and products containing triamterene or hydrochlorothiazide include the following:

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

Rev. 1/92
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References

1. Schnaper HW, Maxwell MH: Efficacy and safety of triamterene/hydrochlorothiazide combinations in mild systemic hypertension. *Am J Cardiol.* 1989;63:32B-36B.
2. Data on file, Lederle Laboratories, Pearl River, NY.

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Advantus™ Pharmaceuticals

February 1993

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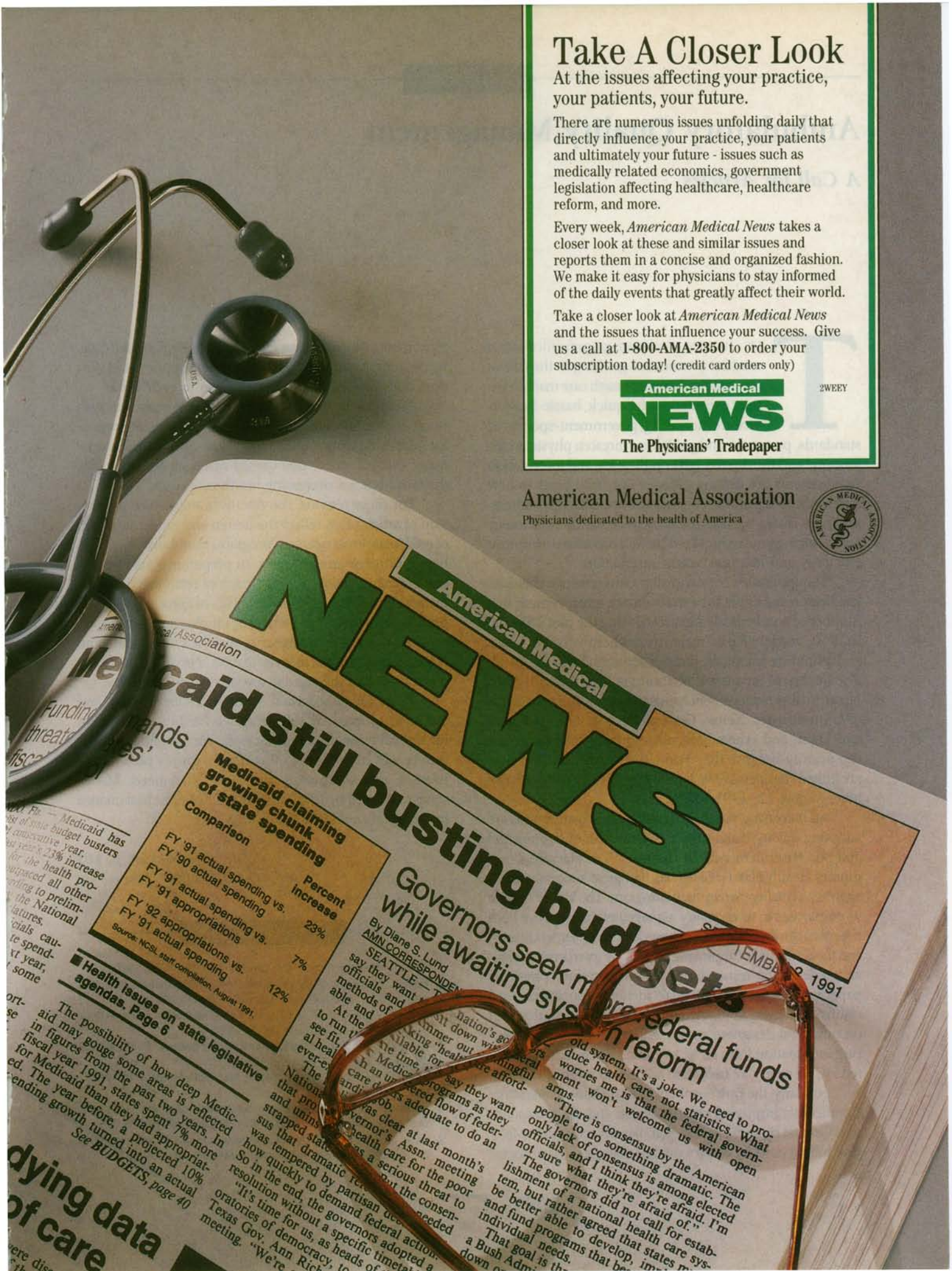
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Governors seek m
while awaiting sys
federal funds
reform
Medicaid claiming growing chunk of state spending
Comparison
Percent increase
FY '91 actual spending vs. FY '90 actual spending 23%
FY '91 actual spending vs. FY '91 appropriations 7%
FY '92 appropriations vs. FY '91 actual spending 12%
Source: NCSL staff compilation, August 1991
Health issues on state legislative agendas. Page 6
dying data
of care

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.

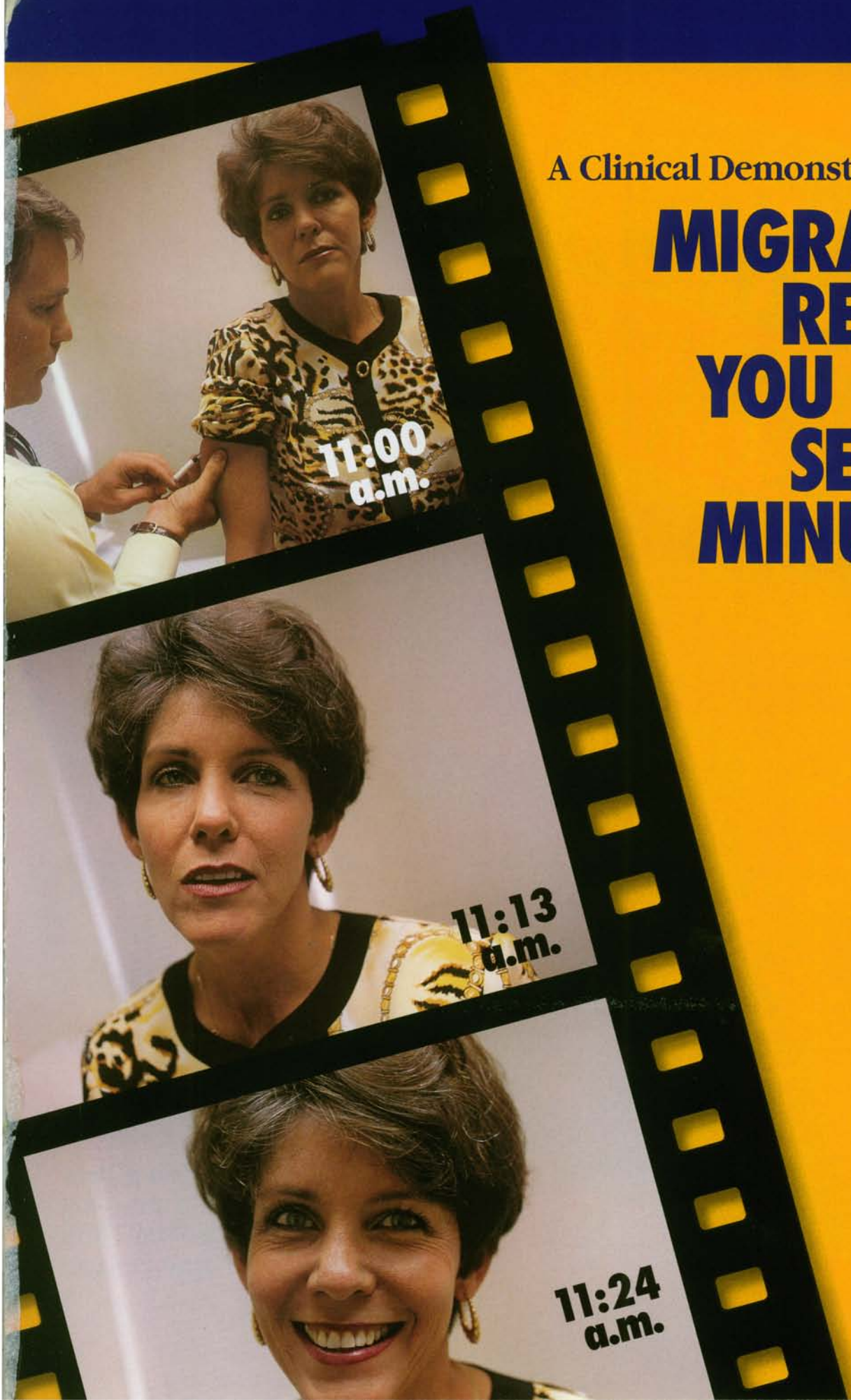
REV Y 03/92

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

FSA-1511 ICI-2870R

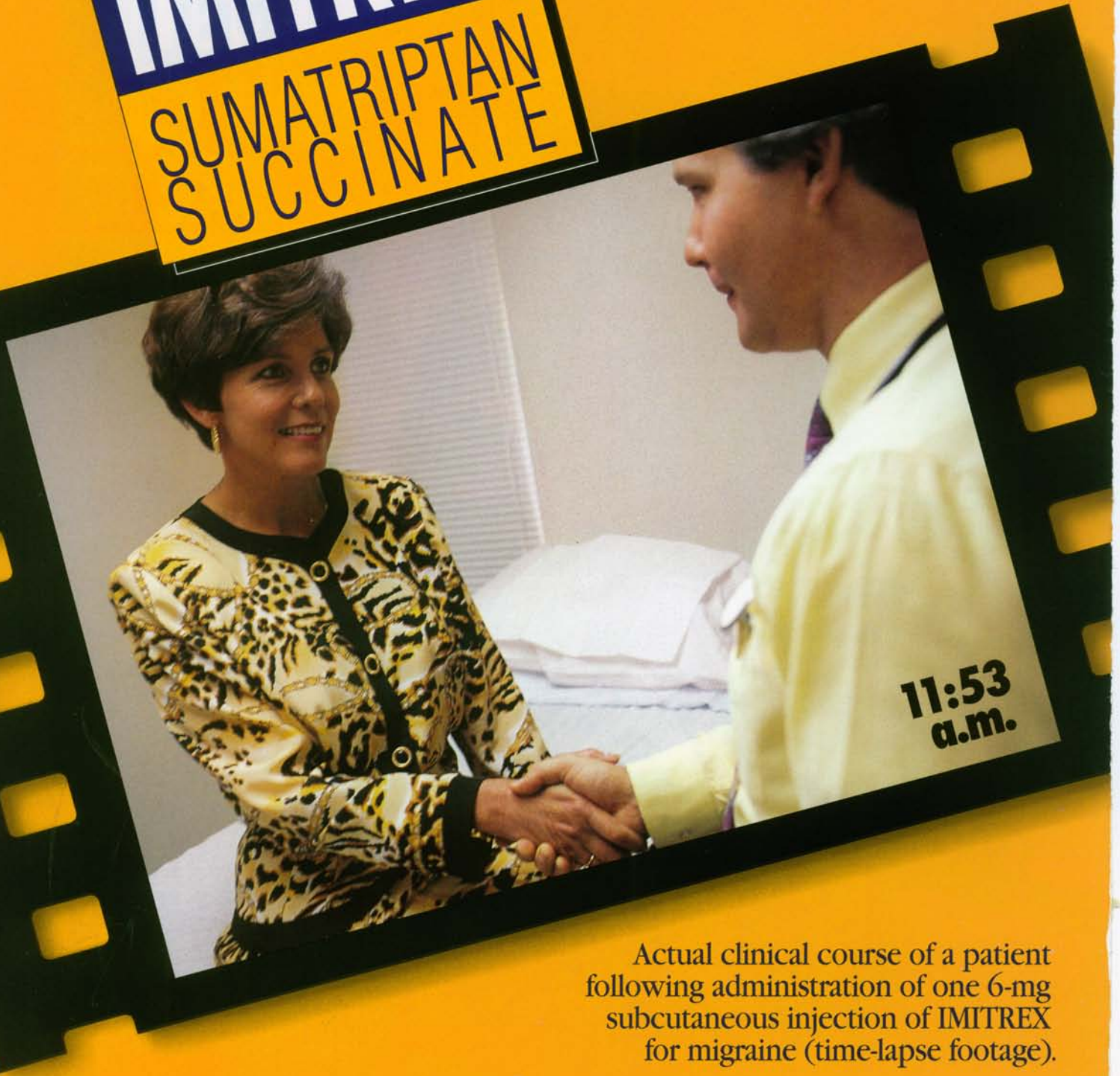
A Clinical Demonstration of

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

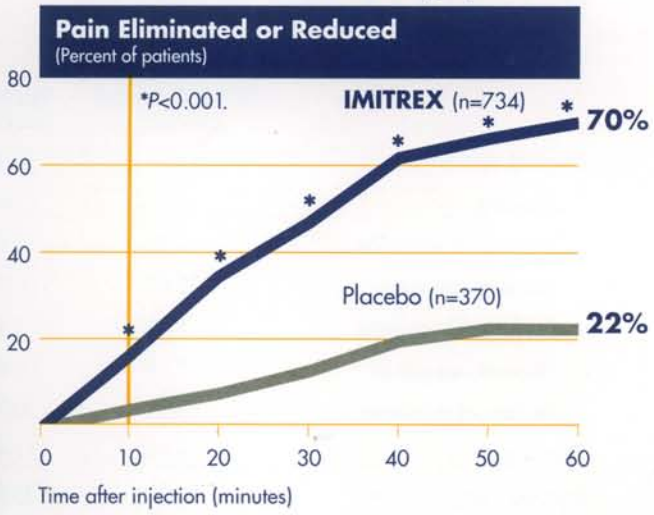
INTRODUCES

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.

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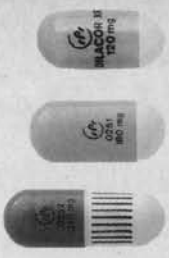

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BRIEF SUMMARY

CONTRAINDICATIONS

Diltiazem hydrochloride is contraindicated in: (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker; (2) patients with second or third degree AV block except in the presence of a functioning ventricular pacemaker; (3) patients with hypotension (less than 90 mmHg systolic); (4) patients who have demonstrated hypersensitivity to the drug; and (5) patients with acute myocardial infarction and pulmonary congestion as documented by X-ray on admission.

WARNINGS

1. Cardiac Conduction. Diltiazem hydrochloride prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second, or third degree AV block (22 of 10,119 patients, or 0.2%); 41% of these 22 patients were receiving concomitant ß-adrenoceptor antagonists versus 17% of the total group. Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single 60 mg dose of diltiazem.

2. Congestive Heart Failure. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction of 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of diltiazem hydrochloride in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

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

4. Acute Hepatic Injury. Mild elevations of serum transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 6 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to diltiazem is uncertain in some cases, but probable in some others (see PRECAUTIONS).

PRECAUTIONS

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

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

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

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

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

Beta-Blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of diltiazem hydrochloride and beta-blockers is usually well-tolerated, but avaiiable data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities. Administration of diltiazem hydrochloride concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and the bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted (see WARNINGS).

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and an 18-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response *in vitro* or *in vivo* in mammalian cell assays or *in vitro* in bacteria. No evidence of impaired fertility was observed in male or female rats at oral doses of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from 4 to 6 times (depending on species) the upper limit of the optimum dosage range in clinical trials (480 mg q.d. or 8 mg/kg q.d. for a 60 kg patient) has resulted in embryo and fetal lethality. These studies have revealed, in one species or another, a propensity to cause abnormalities of the skeleton, heart, retina, and tongue. Also observed were reductions in early individual pup weights and pup survival, prolonged delivery and increased incidence of stillbirths.

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

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

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

ADVERSE REACTIONS

Serious adverse reactions to diltiazem hydrochloride have been rare in studies with other formulations, as well as with Dilacor XR®. It should be recognized, however, that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

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

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

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

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

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

OVERDOSAGE OR EXAGGERATED RESPONSE

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

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

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

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

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

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

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

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

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

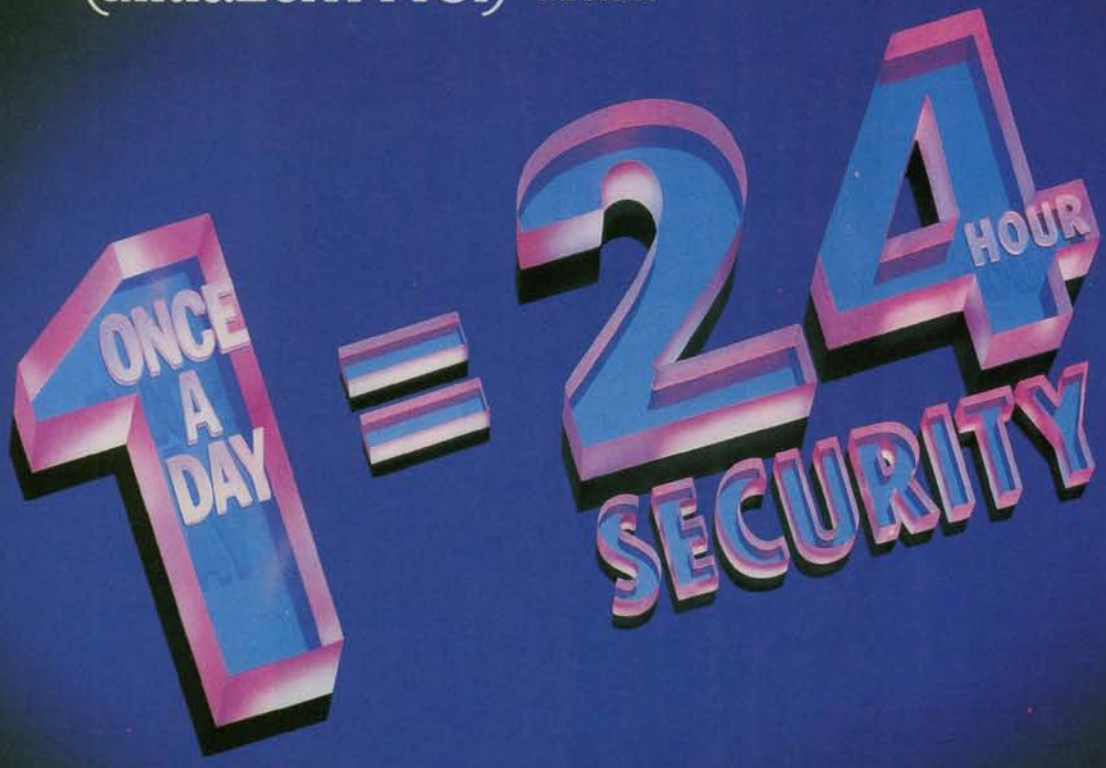
FC# 93-Q21

NEW
120-mg strength
for patients who need the lowest starting dose

Now, *for hypertension*
Once-a-day

DILACOR XR®

(diltiazem HCl) EXTENDED RELEASE CAPSULES



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

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

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

Please see adjacent page for brief summary of prescribing information.

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

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How much of the information you share with your patients really registers with them? After all, they may be worried . . . preoccupied. They listen to what you have to say, but do they *hear* you? By the time they arrive home, they may remember less than you'd like about their medical condition and the treatment you've prescribed for them.

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

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

Training materials include:

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

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

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

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

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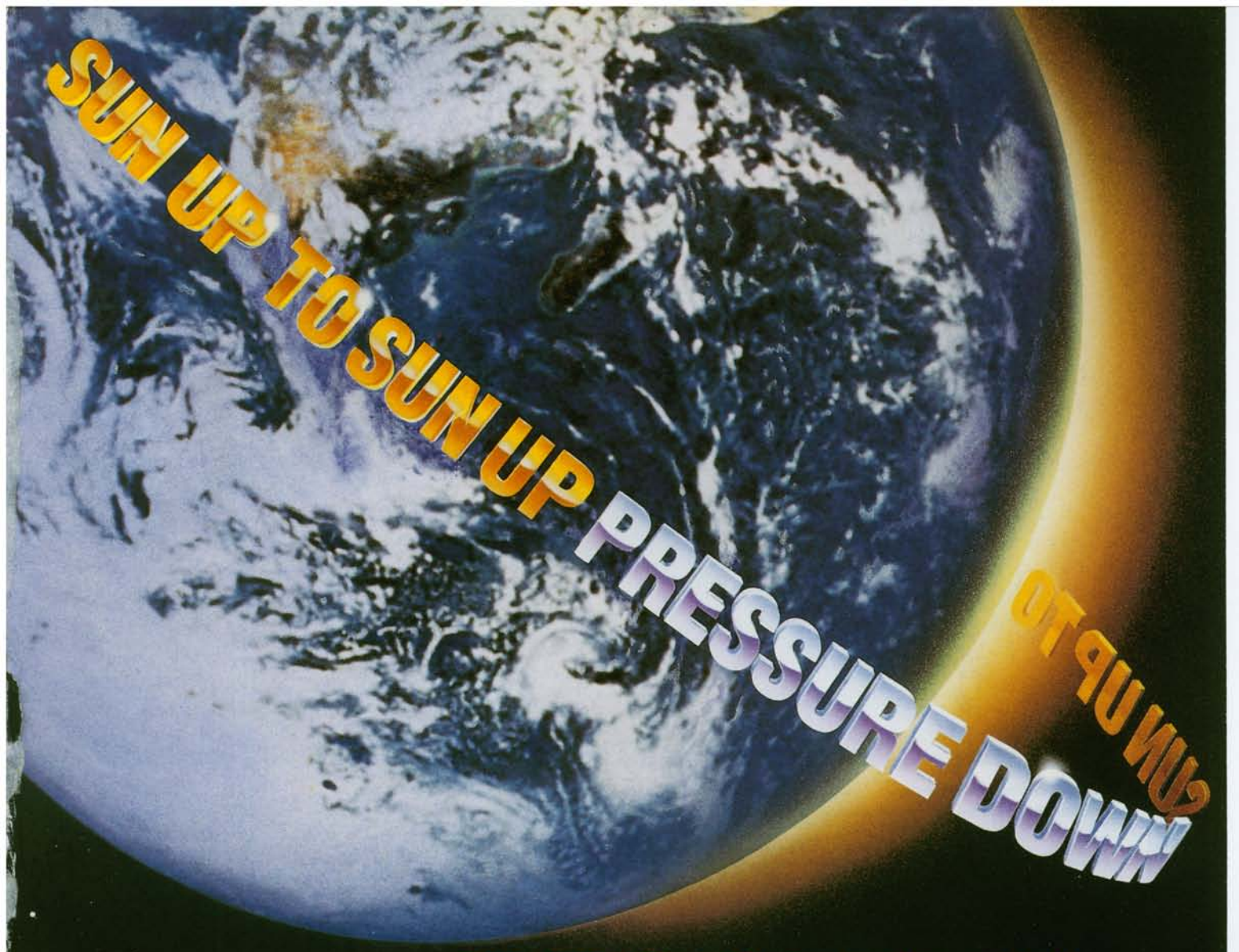
The complete **For Your Protection: The OSHA Regulations on Bloodborne Pathogens** training kit is available for $195, including S & H ($150 for AMA Members, Hospitals, Institutions, Universities, and Government Offices).

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

American Medical Television | American Medical Association

American Medical Television is produced in conjunction with the American Medical Association.



True once-daily antihypertensive control*

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

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

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

ONCE-DAILY

ISOPTIN SR

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

knoll®
BASF Group

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

Please see back for brief summary of prescribing information.

ONCE-DAILY

ISOPTIN® SR

(verapamil HCl) Sustained-Release Tablets

Unsurpassed dosage flexibility

180 mg

The recommended starting/maintenance dose

240 mg

For patients who require a step up in dosage

120 mg

For elderly or small-stature patients who require lower doses

From the originators of verapamil

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BASF Group

Knoll Pharmaceutical Company
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Whippany, New Jersey 07981

I2095/12-92 Printed in USA

Brief Summary of Prescribing Information

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

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

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

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

ADVERSE REACTIONS: Constipation 7.3%, dizziness 3.3%, nausea 2.7%, hypotension 2.5%, headache 2.2%, edema 1.9%, CHF/pulmonary edema 1.8%, fatigue 1.7%, dyspnea 1.4%, bradycardia 1.4%, 2° and 3° AV block 0.8%, rash 1.2%, flushing 0.6% and elevated liver enzymes (see WARNINGS). The following reactions, reported in less than 1.0% of patients, occurred under conditions (open trials, marketing experience) where a causal relationship is uncertain; they are mentioned to alert the physician to a possible relationship: angina pectoris, atrioventricular dissociation, arthralgia and rash, blurred vision, cerebrovascular accident, chest pain, claudication, confusion, diarrhea, dry mouth, ecchymosis or bruising, equilibrium disorders, erythema multiforme, exanthema, gastrointestinal distress, gingival hyperplasia, gynecomastia, hair loss, hyperkeratosis, impotence, increased urination, insomnia, macules, muscle cramps, myocardial infarction, palpitations, paresthesia, psychotic symptoms, purpura (vasculitis), shakiness, somnolence, spotty menstruation, Steven-Johnson syndrome, sweating, syncope, urticaria.

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

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

DOSAGE AND ADMINISTRATION

Essential Hypertension

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

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

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

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

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THE PRAVACHOL® DIRECTION

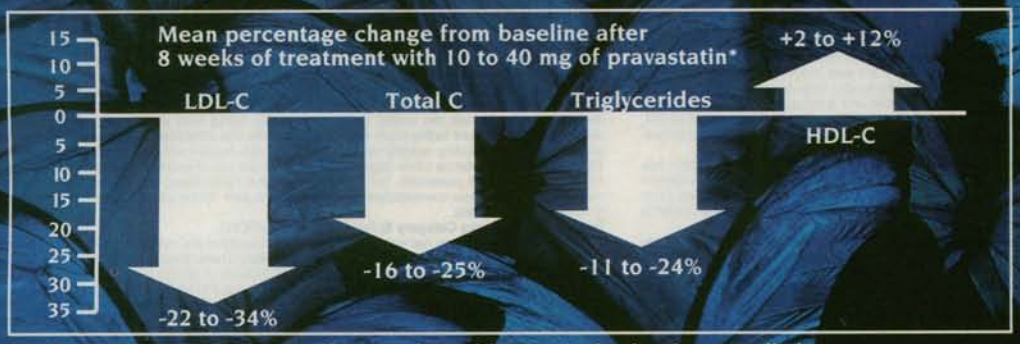
Effective lipid management doesn't have to be tough

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

IN LIPID MANAGEMENT

Effective lipid management—improves key lipids

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



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

Excellent safety/tolerability profile for patients

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

Easy dosing regimen and other patient benefits

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

PRAVACHOL®

pravastatin sodium 20 mg tablets

Bristol-Myers Squibb Company

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

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

PRAVACHOL® (Pravastatin Sodium Tablets)

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

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

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

WARNINGS

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

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

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

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

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

PRECAUTIONS

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

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

Renal Insufficiency. A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3α-hydroxy isomeric metabolite (SQ 31,906). A small increase was seen in mean AUC values and half-life ($t_{1/2}$) for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

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

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

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

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

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

Cimetidine: The $AUC_{0\text{-}12hr}$ for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

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

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

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

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

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

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

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

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

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

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

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

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

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

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

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

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

ADVERSE REACTIONS

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

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

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

*Statistically significantly different from placebo.

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

Skeletal: myopathy, rhabdomyolysis.

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

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

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

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

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

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

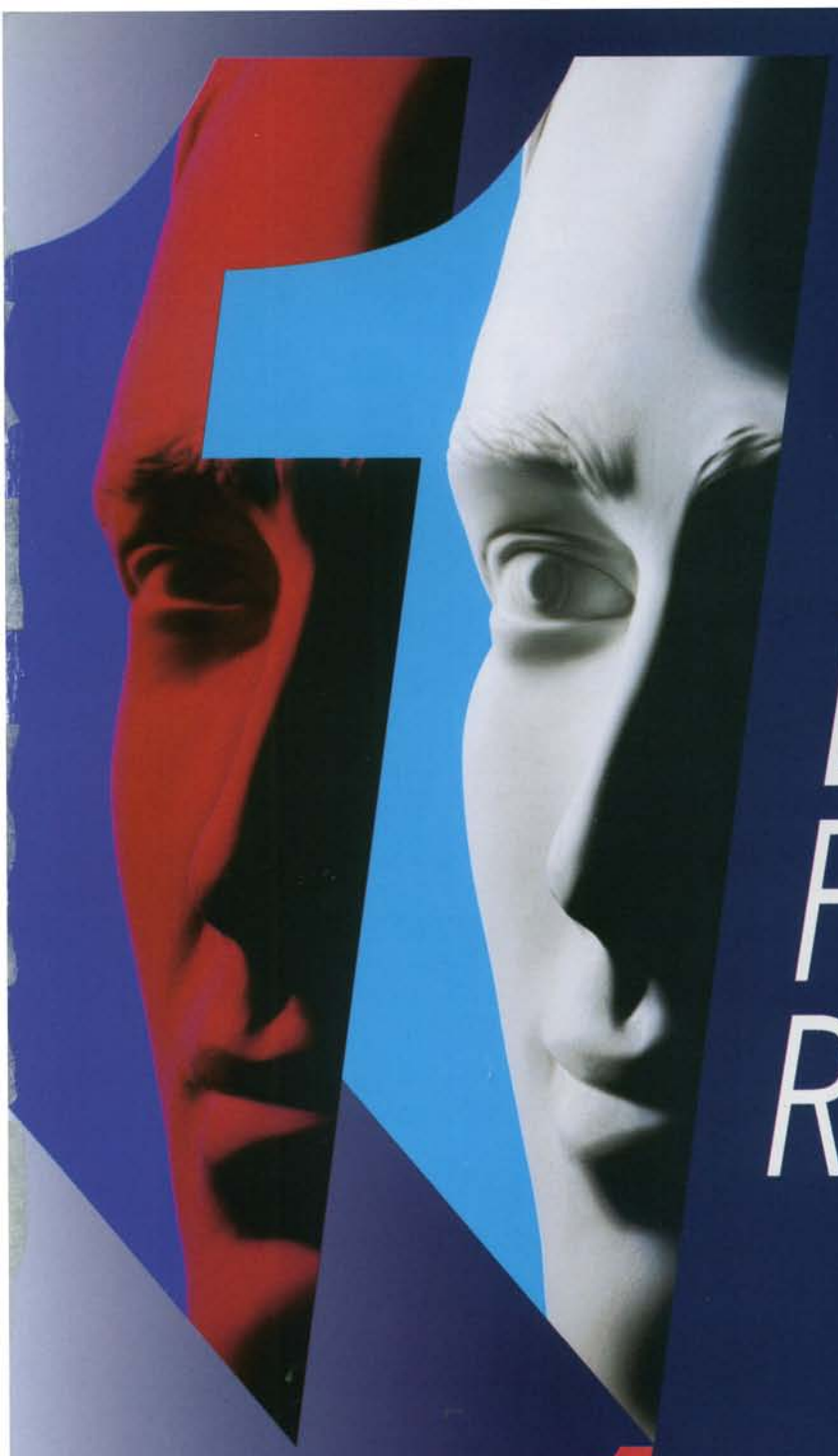
Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

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

OVERDOSAGE

There have been no reports of overdoses with pravastatin.

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



Now, for allergic rhinitis...

ONCE DAILY FOR RELIEF

Once daily for convenience

Once daily for comfort[1,2]

Once daily for unsurpassed safety[3-5]

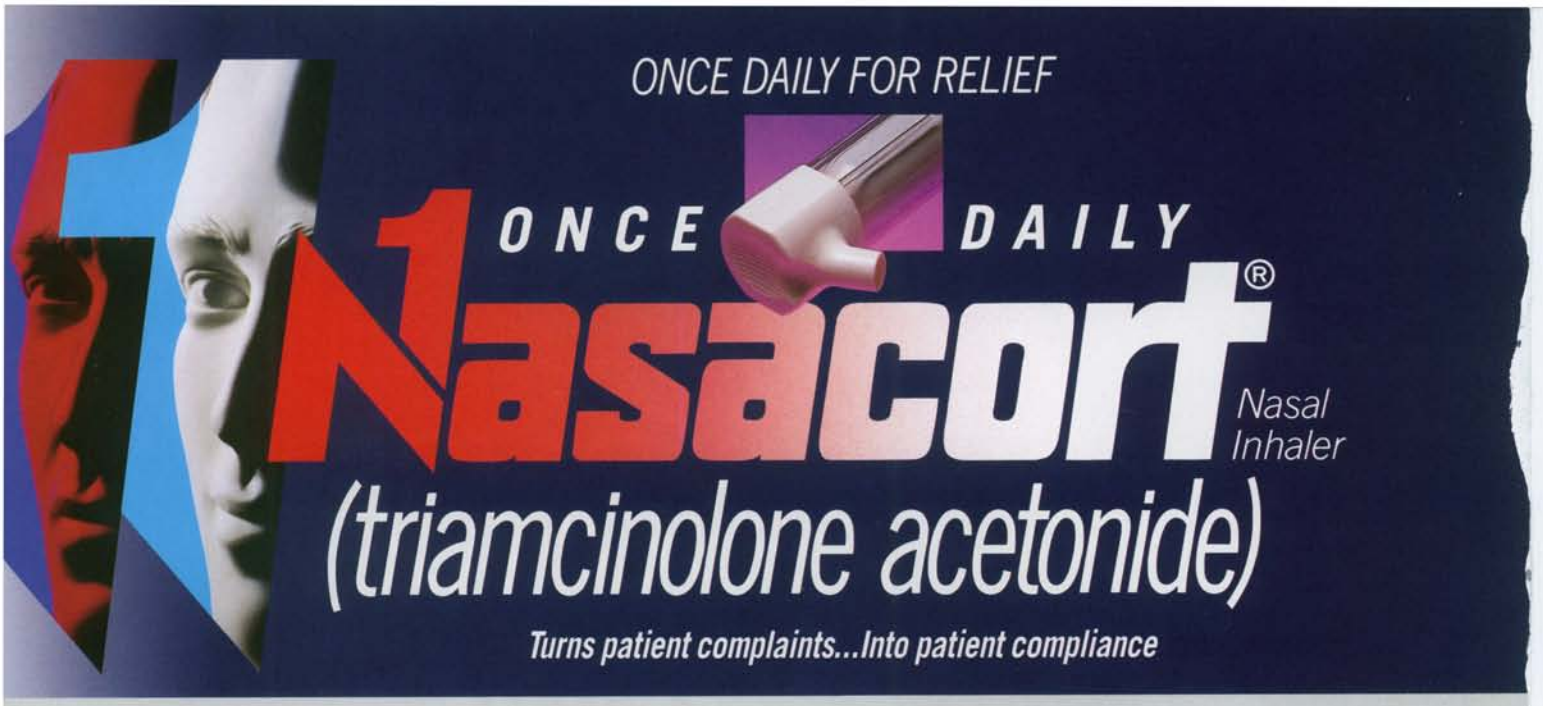
ONCE DAILY

Nasacort® Nasal Inhaler

(triamcinolone acetonide)

Turns patient complaints...Into patient compliance

Please see brief summary of prescribing information on adjacent page.



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

For Intranasal Use Only
Shake Well Before Using

BRIEF SUMMARY

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

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

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

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

PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Please see product circular for full prescribing information.

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

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What do we really know about editorial peer review in scientific publication?

Something, but not enough.

- We know that peer review is widely used, but how widely?
- We know that peer review suffers from bias and conflicts of interest, but what biases and conflicts really matter? And how do we get rid of them?
- We fear that peer review suppresses innovation, but to what extent?
- We know that peer review has existed for years without scientific proof of its worth, but will it hold up under the same rigor and scrutiny we demand of science itself?

To answer many of these questions, editors, scientists, and scholars will gather to present and discuss research findings at the Second International Congress on Peer Review in Biomedical Publication, September 9-11, 1993, at the Fairmont Hotel in Chicago, Illinois.

The Second International Congress on Peer Review in Biomedical Publication

September 9-11, 1993 Chicago, Illinois

Topics will include

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- The relationships between authors, editors, and reviewers, and how each is educated, selected, and evaluated
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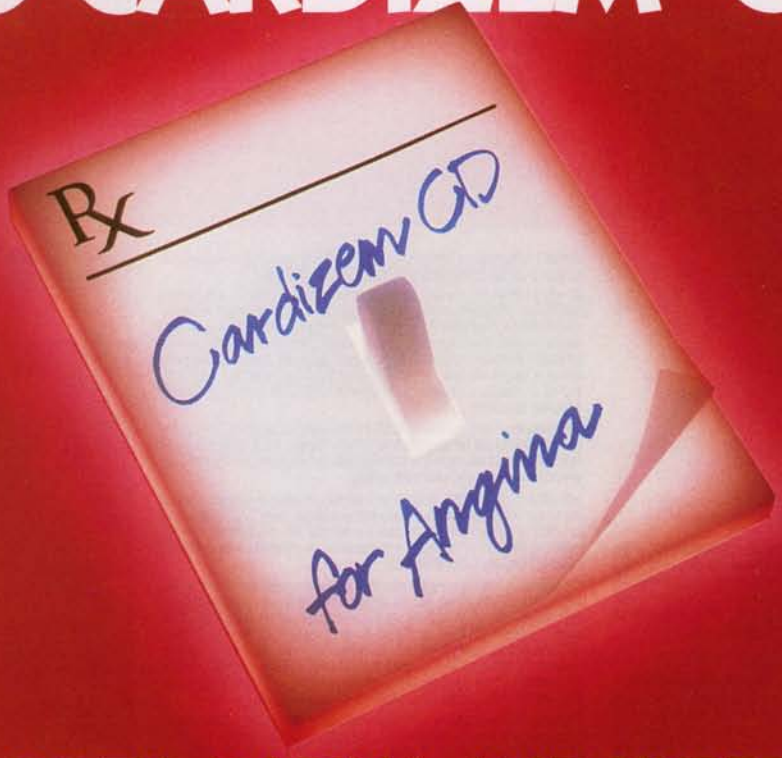
American Medical Association

Physicians dedicated to the health of America

A NEW REASON TO SWITCH TO CARDIZEM® CD



NOW FOR BOTH ANGINA AND HYPERTENSION

One convenient once-daily formulation for both indications

Lower price – 35% lower cost than Cardizem® (diltiazem HCl) tablets*
– 25% lower cost than Cardizem® SR (diltiazem HCl) capsules, based on average wholesale prices (AWP) when dosed on an equivalent mg/day basis.

Easy to transfer patients

- Convert patients on Cardizem tablets or Cardizem SR capsules on a total mg/day basis
- Monitor and titrate if necessary
- Cardizem CD is available in 120-, 180-, 240-, and 300-mg capsules

ONCE A DAY

THE ONE CARDIZEM® CD (diltiazem HCl)

* Based on *Red Book*, October 1992.
Cardizem® tablets, for angina, are available as 30, 60, 90, and 120 mg.
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Please see the brief summary of prescribing information on an adjacent page.

CCDAH828/A7514

1025S2

Now for both angina and hypertension

ONCE-A-DAY CARDIZEM® CD

(diltiazem HCl)

Switch from Cardizem (diltiazem HCl) tablets on a total mg/day basis*

For new patients, a recommended starting dose:

- One 180-mg capsule qd

*Monitor and titrate.

Brief Summary of
Prescribing Information as of October 1992 (2)

CARDIZEM® CD
(diltiazem hydrochloride)
Capsules

Brief Summary of
Prescribing Information as of January 1991

CARDIZEM® SR
(diltiazem hydrochloride)
Sustained Release Capsules

Brief Summary of
Prescribing Information as of January 1991

CARDIZEM®
(diltiazem hydrochloride)
Tablets

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

1. **Cardiac Conduction**. CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3,290 patients or 0.40%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure**. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of CARDIZEM (diltiazem hydrochloride) in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.
3. **Hypotension**. Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury**. Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters of renal and hepatic function should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.
Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

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

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

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

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

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and a single dose of diltiazem 60 mg. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

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

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

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

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

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

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

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

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.
In domestic placebo-controlled angina trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.
The adverse events described below represent events observed in clinical studies of hypertensive patients receiving either CARDIZEM Tablets or CARDIZEM SR Capsules as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients taking CARDIZEM Tablets or CARDIZEM SR Capsules studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and first-degree AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related.

Double Blind Placebo-Controlled Hypertension Trials

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

The following table presents the most common adverse reactions reported in placebo-controlled angina and hypertension trials in patients receiving CARDIZEM CD up to 360 mg with rates in placebo patients shown for comparison.

CARDIZEM CD Capsules Placebo-Controlled Angina and Hypertension Trials Combined

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

In clinical trials of CARDIZEM CD Capsules, CARDIZEM Tablets, and CARDIZEM SR Capsules involving over 3200 patients, the most common events (ie, greater than 1%) were edema (4.6%), headache (4.6%), dizziness (3.5%), asthenia (2.6%), first-degree AV block (2.4%), bradycardia (1.7%), flushing (1.4%), nausea (1.4%), and rash (1.2%).
In addition, the following events were reported infrequently (less than 1%) in angina or hypertension trials:
Cardiovascular: Angina, arrhythmia, AV block (second- or third-degree), bundle branch block, congestive heart failure, ECG abnormalities, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles
Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor
Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeusia, dyspepsia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hepatic warnings), thirst, vomiting, weight increase
Dermatological: Petechiae, photosensitivity, pruritus, urticaria
Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties
The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, erythema multiforme, exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well-documented cases of generalized rash, characterized as leukocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and CARDIZEM therapy is yet to be established.

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

CARDIZEM® SR
Prescribing Information as of January 1991

CARDIZEM®
Prescribing Information as of January 1991

Marion Merrell Dow Inc.
Kansas City, Missouri 64114

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

CCDAH828/A7514

1025R2

"We're pretty certain that we don't want more children, but we wanted to leave the possibility open."

Kathy Hill
Jacksonville, FL

NORPLANT® SYSTEM
levonorgestrel implants

Lasts 5 years...yet is reversible

Serious as well as minor side effects may occur. The most common side effect which has been observed is menstrual bleeding irregularities.

Please see brief summary of prescribing information on the following page.

NORPLANT® SYSTEM

levonorgestrel implants

Lasts five years…yet is reversible

BRIEF SUMMARY OF PRESCRIBING INFORMATION. CONSULT THE PACKAGE LITERATURE FOR FULL PRESCRIBING INFORMATION.

Indications and Usage

The NORPLANT SYSTEM is indicated for the prevention of pregnancy and is a long-term (up to 5 years) reversible contraceptive system. The capsules should be removed by the end of the 5th year. New capsules may be inserted at that time if continuing contraceptive protection is desired.

Contraindications

1. Active thrombophlebitis or thromboembolic disorders. 2. Undiagnosed abnormal genital bleeding. 3. Known or suspected pregnancy. 4. Acute liver disease; benign or malignant liver tumors. 5. Known or suspected carcinoma of the breast.

Warnings

A. WARNINGS BASED ON EXPERIENCE WITH THE NORPLANT SYSTEM

1. *Bleeding Irregularities* — Most women can expect some variation in menstrual bleeding patterns. Irregular menstrual bleeding, intermenstrual spotting, prolonged episodes of bleeding and spotting, and amenorrhea may occur, and could mask symptoms of cervical or endometrial cancer. Overall, these irregularities diminish with continued use. Because amenorrhea may occur, missed menstrual periods cannot serve as the only identifier of early pregnancy. Perform pregnancy tests whenever pregnancy is suspected. If pregnancy occurs, the capsules must be removed. Hemoglobin concentrations found in clinical trials generally indicated that reduced menstrual blood loss is associated with NORPLANT SYSTEM use. Blood loss resulting in hemoglobin values consistent with anemia occurred rarely.

2. *Delayed Follicular Atresia* — Atresia of the follicle is sometimes delayed, resulting in enlarged follicles that are clinically indistinguishable from ovarian cysts. In the majority of women, enlarged follicles disappear spontaneously. Rarely, they twist or rupture and surgical intervention may be required.

3. *Ectopic Pregnancies* — Ectopic pregnancies have occurred among NORPLANT SYSTEM users, although clinical studies have shown no increase in the rate of ectopic pregnancies per year among NORPLANT SYSTEM users as compared with users of no method or of IUDs. The incidence among NORPLANT SYSTEM users (1.3 per 1000 woman-years) was significantly below the rate estimated for noncontraceptive users in the U.S. (2.7 to 3.0 per 1000 woman-years). Ectopic pregnancy risk may increase with duration of NORPLANT SYSTEM use and increased weight of the user. Rule out ectopic pregnancy in any patient presenting with lower-abdominal pain.

4. *Breast-feeding* — Steroids are not the contraceptives of first choice for lactating women. Levonorgestrel has been identified in breast milk. Limited data suggests no significant effects on infant growth or health when mothers used the NORPLANT SYSTEM beginning 6 weeks after parturition.

5. *Foreign-body Carcinogenesis* — Rarely, cancers occur at foreign-body intrusion sites or old scars. None has been reported in NORPLANT SYSTEM clinical trials and risk to users is judged to be minimal.

6. *Thromboembolic Disorders* — Remove capsules if active thrombophlebitis or thromboembolic disease develops. With prolonged immobilization removal should be considered.

B. WARNINGS BASED ON EXPERIENCE WITH COMBINATION (PROGESTIN PLUS ESTROGEN) ORAL CONTRACEPTIVES (OCs)

Note: Many of the side effects or risks listed below are thought to be estrogen-related; the association of the NORPLANT SYSTEM progestin-only method to these risks is unknown.

1. *Cigarette Smoking* — Cigarette smoking increases the risk of serious cardiovascular side effects from combined OC use. Risk increases with age and heavy smoking (≥15 cigarettes/day) and is quite marked in women over 35 years old.

2. *Elevated Blood Pressure* — Increase in blood pressure has been reported in combination OC users; prevalence increases with long exposure.

3. *Thromboembolic Disorders and Other Vascular Problems* — An increased risk of thromboembolic and thrombotic disease is associated with combination OC use. Estimate of relative risk is 4- to 11-fold higher for users vs. nonusers.

Cerebrovascular Disorders: Combination OCs increase the relative and attributable risk of cerebrovascular events (thrombotic and hemorrhagic strokes). Generally, risk is greatest among hypertensive women > 35 years of age who smoke.

Myocardial Infarction (MI): An increased risk of MI has been attributed to combined OC use. This is thought to be primarily thrombotic in origin and related to the estrogen component. Increased risk occurs primarily in smokers or women with other underlying risk factors for coronary-artery disease. Relative risk of heart attack for combined OC users is estimated as 2 to 6 times that for nonusers. Absolute risk is very low for women under 30 years old.

Studies indicate a significant trend toward higher MI and stroke rates with increased progestin doses in combination OCs. However, recent data indicated no increased MI risk with past use of levonorgestrel-containing OCs.

4. *Carcinoma* — Recent evidence in the literature suggests no association between OC use and increased risk of breast cancer in the overall population of users. The Cancer and Steroid Hormone (CASH) study also showed no latent effect on breast cancer risk for at least a decade following long-term use. Some of these same studies have shown an increased relative risk of breast cancer in certain subgroups; no consistent pattern has been identified. Some studies suggest an association between combination OCs and an increase in the risk of cervical intra-epithelial neoplasia in some populations of women. The extent to which such findings may be due to differences in sexual behavior and other factors remains controversial. A cause-and-effect relationship between combined OC use and breast or cervical cancer has not been established. Combination OCs may decrease ovarian and endometrial cancer risk. Irregular bleeding patterns associated with NORPLANT SYSTEM use could mask cervical or endometrial cancer symptoms.

5. *Hepatic Tumors* — Hepatic adenomas are associated with combination OC use; estimated incidence is 3 events per 100,000 users per year. Risk increases after 4 or more years of use. Hepatic adenomas are benign but may rupture and cause death through intra-abdominal hemorrhage.

6. *Ocular Lesions* — Retinal thrombosis is associated with OC use and is believed to be related to the estrogen component. However, NORPLANT SYSTEM capsules should be removed if there is unexplained partial or complete vision loss; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Undertake appropriate diagnostic and therapeutic measures immediately.

7. *Use Before or During Early Pregnancy* — Extensive epidemiological studies reveal no increased risk of birth defects when OCs are used prior to pregnancy. Studies also do not suggest a teratogenic effect when taken inadvertently during early pregnancy. No evidence suggests that risk with NORPLANT SYSTEM use is different.

8. *Gallbladder Disease* — Early studies reported an increased lifetime relative risk of gallbladder surgery in OC or estrogen users. More recent studies, however, indicate that the relative risk of gallbladder disease with OC use may be minimal; this may be related to use of OCs with less estrogen and progestin content.

Precautions

GENERAL:

1. *Physical Examination and Follow-up* — A complete medical history and physical examination should be taken prior to implantation or reimplantation of NORPLANT SYSTEM capsules and at least annually during its use. Exams should include special reference to the implant site, blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests. Rule out malignancy in cases of undiagnosed, persistent or recurrent abnormal vaginal bleeding. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

2. *Carbohydrate Metabolism* — Altered glucose tolerance is found in some combination and progestin-only OC users. Effects of NORPLANT SYSTEM on carbohydrate metabolism appear minimal. Observe diabetic and prediabetic patients carefully while using the NORPLANT SYSTEM. Follow women being treated for hyperlipidemias closely if using the NORPLANT SYSTEM. Some progestins may elevate LDL and may render control of hyperlipidemias more difficult. (See **Warnings**.)

3. *Liver Function* — Consider removing capsules if jaundice develops. Steroid hormones may be poorly metabolized in patients with impaired liver function.

4. *Fluid Retention* — Steroid contraceptives may cause some degree of fluid retention. Prescribe with caution, and careful monitoring, in patients with conditions possibly aggravated by fluid retention.

5. *Emotional Disorders* — Consider removing capsules if significant depression occurs since the symptom may be drug-related. Observe carefully those with history of depression and consider removal if depression recurs to a serious degree.

6. *Contact Lenses* — Contact-lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

7. *Insertion and Removal* — Insertion is advised during the first 7 days of the cycle or immediately following abortion to insure that the woman is not pregnant and to assure contraceptive effectiveness during first cycle of use. Capsules may be inserted at any time during the cycle provided pregnancy has been excluded and a nonhormonal contraceptive method is used for the remainder of the cycle. Insertion is not recommended before 6 weeks postpartum in breast-feeding women. Follow insertion and removal instructions closely. Healthcare professionals are strongly advised to be instructed in the procedures before they attempt them. Proper insertion just under the skin facilitates removals; proper insertion and removal should result in minimal scarring. If all capsules cannot be removed at first attempt, attempt removal later when the site has healed. Bruising may occur at implant site during insertion or removal. Hyperpigmentation may occur over implant site but is usually reversible following removal. **See Full Prescribing Information for Detailed Insertion/Removal Instructions.**

8. *Infections* — Implant site infection has been uncommon (0.7%); aseptic technique and proper insertion/removal reduces possibility of infection. Institute treatment if infection occurs; remove capsules if infection persists.

9. *Expulsion* — Expulsion of capsules was uncommon; frequency increased when capsule placement was extremely shallow, was too close to incision, or when infection was present. Replace expelled capsule with new sterile capsule. Treat and cure any infection before replacement. Contraceptive efficacy may be inadequate with fewer than 6 capsules.

10. *Provisions for Removal* — Advise women that capsules may be removed at any time for any reason. Personnel instructed in removal technique should perform removal on request or at the end of 5 years of usage. Upon removal, dispose of capsules in accordance with Centers for Disease Control Guidelines for biohazardous waste.

DRUG INTERACTIONS: Reduced efficacy (pregnancy) in NORPLANT SYSTEM users has been reported when phenytoin or carbamazepine were used concomitantly. Warn NORPLANT SYSTEM users of possible decreased efficacy with use of related drugs.

DRUG/LABORATORY TEST INTERACTIONS: 1. Sex-hormone-binding globulin concentrations are decreased. 2. Thyroxine concentrations may be slightly decreased and triiodothyronine uptake increased.

CARCINOGENESIS: See **Warnings** section and Full Prescribing Information.

PREGNANCY: Pregnancy Category X. See **Warnings** section and Full Prescribing Information.

NURSING MOTHERS: See **Warnings** section and Full Prescribing Information.

INFORMATION FOR THE PATIENT: See Patient Labeling. Provide copy of patient labeling to the patient. Advise patients that Prescribing Information is available upon request. Inform prospective users of risks and benefits associated with NORPLANT SYSTEM use, with other forms of contraception, with no contraception, and about insertion/removal procedures. Informed consent from all patients may be desired in light of techniques involved with insertion and removal.

Adverse Reactions

The following have been associated with the NORPLANT SYSTEM during first year of use: many bleeding days or prolonged bleeding (27.6%); spotting (17.1%); amenorrhea (9.4%); irregular (onsets of) bleeding (7.6%); frequent bleeding onsets (7.0%); scanty bleeding (5.2%); pain or itching near implant site - usually transient - (3.7%); infection at implant site (0.7%); removal difficulties affecting subjects - based on 849 removals - (6.2%).

Controlled clinical studies suggest that the following, occurring during the first year, are probably associated with NORPLANT SYSTEM use: headache; nervousness; nausea; dizziness; adnexal enlargement; dermatitis; acne; change of appetite; mastalgia; weight gain; hirsutism, hypertrichosis, and scalp-hair loss. The following were reported with a frequency of 5% or greater during the first year and possibly may be related to NORPLANT SYSTEM use: breast discharge; cervicitis; musculoskeletal pain; abdominal discomfort; leukorrhea; vaginitis.

Overdosage

Overdosage may cause fluid retention with its associated effects and uterine bleeding irregularities.

Dosage and Administration

The NORPLANT SYSTEM consists of six Silastic® capsules, each containing 36 mg of the progestin, levonorgestrel. The total administered (implanted) dose is 216 mg. Implantation of all six capsules should be performed during the first 7 days of the onset of menses by a healthcare professional instructed in the NORPLANT SYSTEM insertion technique. Insertion is subdermal in the midportion of the upper arm about 8 to 10 cm above the elbow crease. Distribution should be in a fanlike pattern, about 15 degrees apart, for a total of 75 degrees. Proper insertion will facilitate later removal. **(See Full Prescribing Information for Detailed Insertion/Removal Instructions.)**

CI 4064-1 12/10/90

Worldwide Leadership in Female Healthcare™

WYETH-AYERST LABORATORIES
Philadelphia, PA 19101

Encouragement

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

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

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

The Paget's Disease Foundation, Inc.

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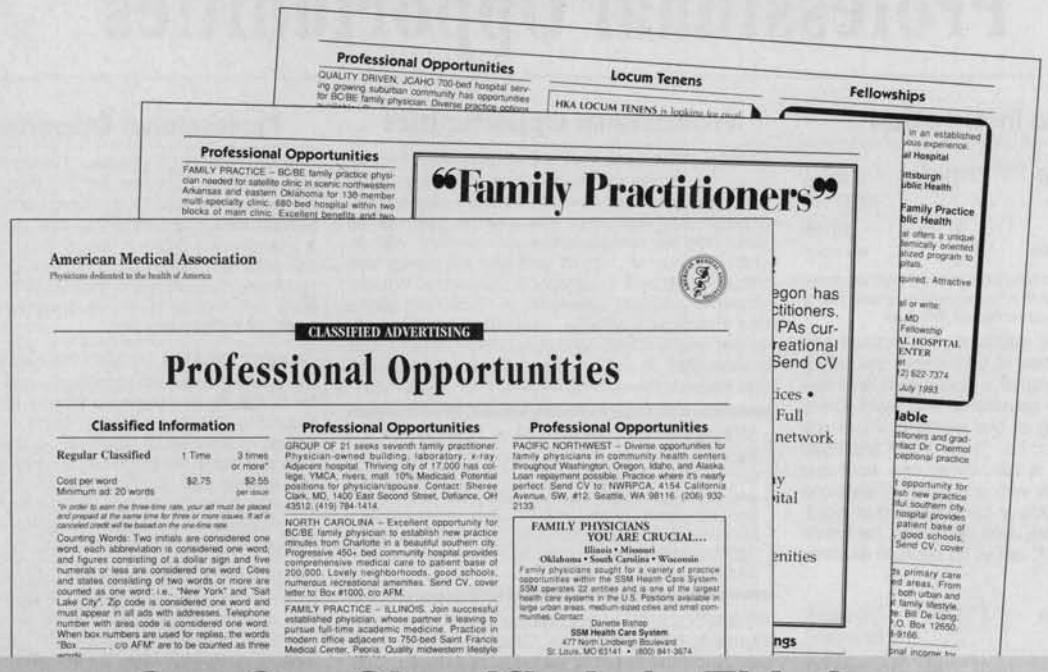

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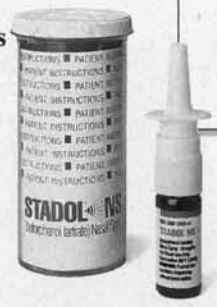
STADOL® NS™
(butorphanol tartrate) Nasal Spray

Acute Pain Relief, Delivered in Minutes



Rx

Stadol NS
1 bottle
Sig: Spray only once into only one nostril. Repeat in 1 hour if needed; additional doses q 3–4 hours PRN

Brief Summary

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

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

WARNINGS

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

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

PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Pregnancy
Pregnancy Category C

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

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

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

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

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

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

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

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

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

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

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

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

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

CARDIOVASCULAR: VASODILATION*, PALPITATIONS

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

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

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

SKIN AND APPENDAGES: sweating/clammy*, pruritus

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

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

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

CARDIOVASCULAR: hypotension

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

SKIN AND APPENDAGES: rash/hives

UROGENITAL: impaired urination

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

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

BODY AS A WHOLE: edema

CARDIOVASCULAR: hypertension

NERVOUS: *convulsion, delusions*, depression

RESPIRATORY: *apnea*, shallow breathing

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

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

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

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

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

OVERDOSAGE

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CAUTION: Federal law prohibits dispensing without prescription.

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A4-K004-4-93

MIGRAINE PAIN
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RELIEVED

...In Minutes

- Effectively relieves acute migraine pain[1]
- Delivers the efficacy of an injectable opioid analgesic with the convenience of a nasal spray
- Unique nasal spray delivery allows administration even in the presence of nausea and vomiting
- Rapid onset of pain relief—within 15 minutes[1]
- Somnolence (43%) is the most frequently reported side effect*
- Not a federally controlled substance

STADOL® NS™

(butorphanol tartrate) Nasal Spray

Acute Pain Relief, Delivered in Minutes

*Across all clinical trials, including STADOL® Injectable and STADOL NS.[2] Patients should not perform hazardous tasks (eg, driving, operating machinery). Alcohol should not be consumed while using STADOL NS.

REFERENCES

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

Please see brief summary of prescribing information on following page.

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