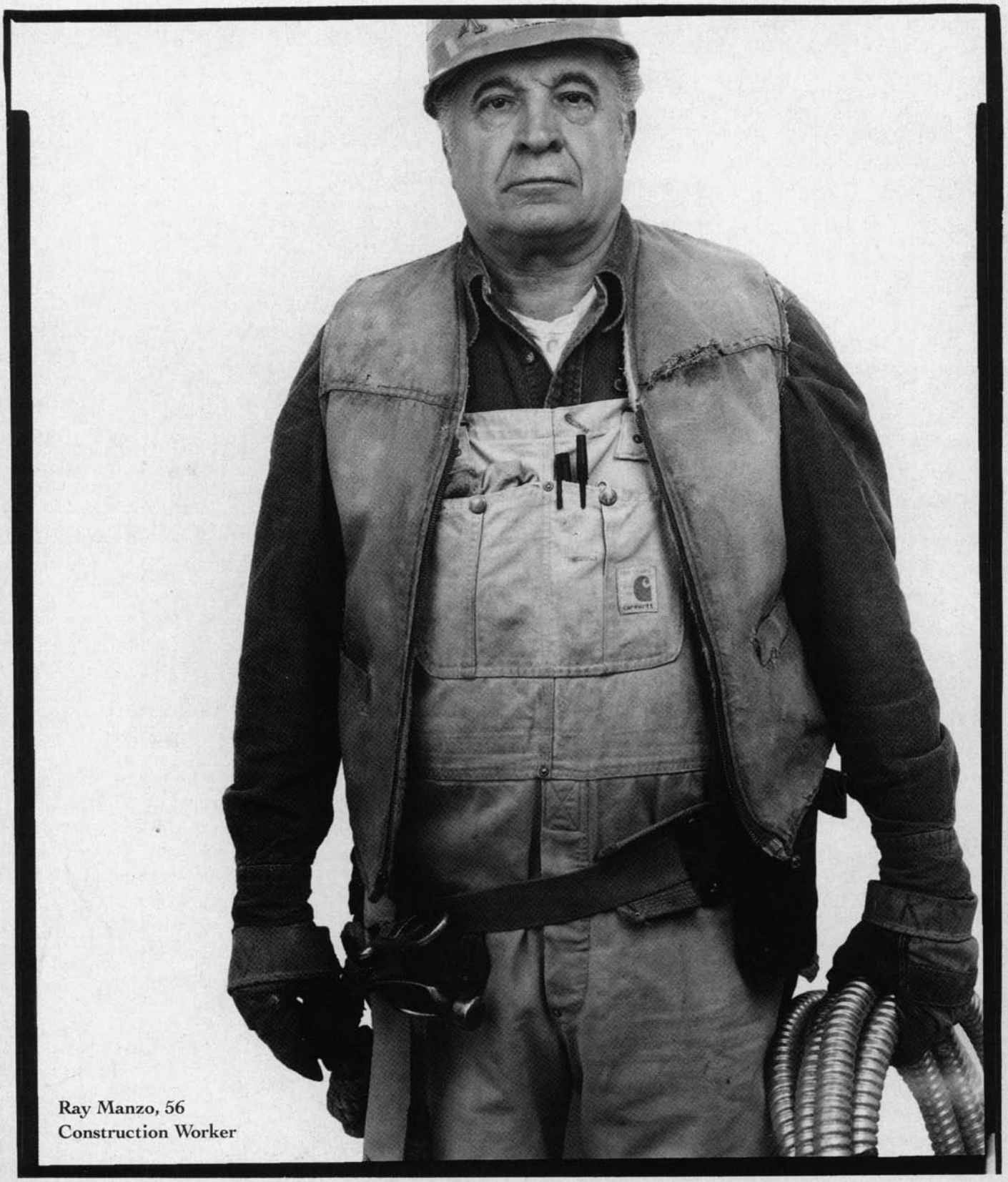


Ray Manzo, 56
Construction Worker

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]

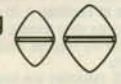
TOUGH PHYSICAL WORK.

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

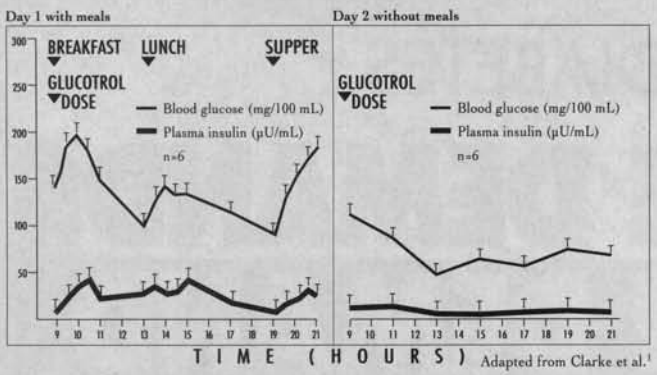


As with all sulfonylureas, hypoglycemia may occur.

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.

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

RGCO28A93

Pfizer Pratt

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

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FAMILY MEDICINE

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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.

Brief Summary

VERELAN®
Verapamil HCl
Sustained-Release Pellet-Filled Capsules

For complete Prescribing Information, consult package insert.

CLINICAL PHARMACOLOGY

Food does not affect the extent or rate of the absorption of verapamil from the controlled release VERELAN capsule.

Atrioventricular block can occur in patients without preexisting condition defects (see **WARNINGS**).

Acceleration of ventricular rate and/or ventricular fibrillation has been reported in patients with atrial flutter or atrial fibrillation and a coexisting accessory AV pathway following administration of verapamil (see **WARNINGS**).

In patients with hepatic insufficiency, metabolism is delayed and elimination half-life prolonged up to 14 to 16 hours (see **PRECAUTIONS**), the volume of distribution is increased, and plasma clearance reduced to about 30% of normal.

CONTRAINDICATIONS

Severe LV dysfunction (see **WARNINGS**), hypotension (systolic pressure <90 mmHg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), second- or third-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), (see **WARNINGS**), hypersensitivity to verapamil.

WARNINGS

Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction <30%) or moderate-to-severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta blocker. Control milder heart failure with optimum digitalization and/or diuretics before VERELAN is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported.

Several cases of hepatocellular injury have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving IV verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (second- or third-degree, 0.8%). Development of marked first-degree block or progression to second- or third-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, second-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

PRECAUTIONS

Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Verapamil has been given concomitantly with short- and long-acting nitrates without any undesirable drug interactions. Interaction between cimetidine and chronically administered verapamil has not been studied. In healthy volunteers, clearance of verapamil was reduced or unchanged. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully.

Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporine. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. **Pregnancy Category C:** There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use. Safety and efficacy of verapamil in children below the age of 18 years have not been established.

ADVERSE REACTIONS

Reversible (upon discontinuation of verapamil) nonobstructive, paralytic ileus has been infrequently reported in association with the use of verapamil.

In clinical trials with 285 hypertensive patients on VERELAN for more than 1 week, the following adverse reactions were reported: constipation (7.4%); headache (5.3%); dizziness (4.2%); lethargy (3.2%); dyspepsia (2.5%); rash (1.4%); ankle edema (1.4%); sleep disturbance (1.4%); myalgia (1.1%). In clinical trials of other formulations of verapamil HCl (N = 4,954), the following reactions have occurred at rates greater than 1.0%: constipation (7.3%); dizziness (3.3%); nausea (2.7%); hypotension (2.5%); edema (1.9%); headache (2.2%); rash (1.2%); CHF/pulmonary edema (1.8%); fatigue (1.7%); bradycardia (HR<50/min) (1.4%); AV block-total 1°, 2°, 3° (1.2%); 2° and 3° (0.8%); flushing (0.6%); elevated liver enzymes (see **WARNINGS**).

The following reactions, reported in 1.0% or less of patients, occurred under conditions (open trials, marketing experience) where a causal relationship is uncertain. **Cardiovascular:** angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope. **Digestive System:** diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia. **Hemic and Lymphatic:** ecchymosis or bruising. **Nervous System:** cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence. **Respiratory:** dyspnea. **Skin:** arthralgia and rash, exanthema, hair loss, hyperkeratosis, maculae, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme. **Special Senses:** blurred vision. **Urogenital:** gynecomastia, impotence, increased urination, spotty menstruation.

Rev. 1/92
20801-92

Lederle

Manufactured for
LEDERLE LABORATORIES DIVISION
American Cyanamid Company
Pearl River, NY 10965

by ELAN PHARMACEUTICAL RESEARCH CORP.
Gainesville, GA 30501

Advantus™ Pharmaceuticals

WYETH-AYERST LABORATORIES

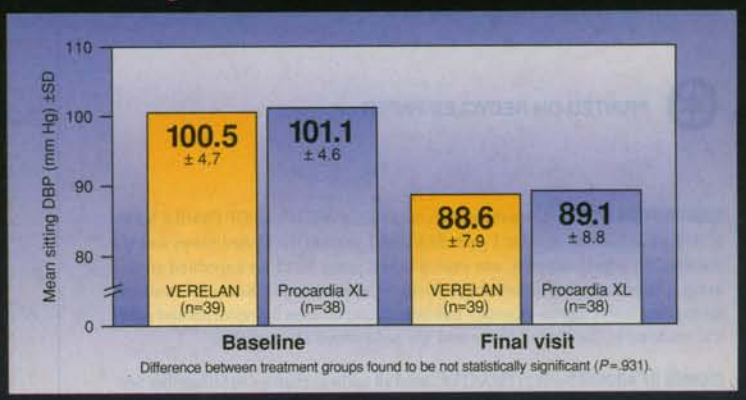
A·H·ROBINS

September 1992 Printed in USA 5150-2

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. 8, AUG 1993

American Medical Association
Physicians dedicated to the health of America


RELAFEN®
nabumetone
SB
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Pharmaceuticals
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Now, for allergic rhinitis...

ONCE DAILY FOR RELIEF

Once daily for convenience

Once daily for comfort[1,2]

Once daily for unsurpassed safety[3-5]

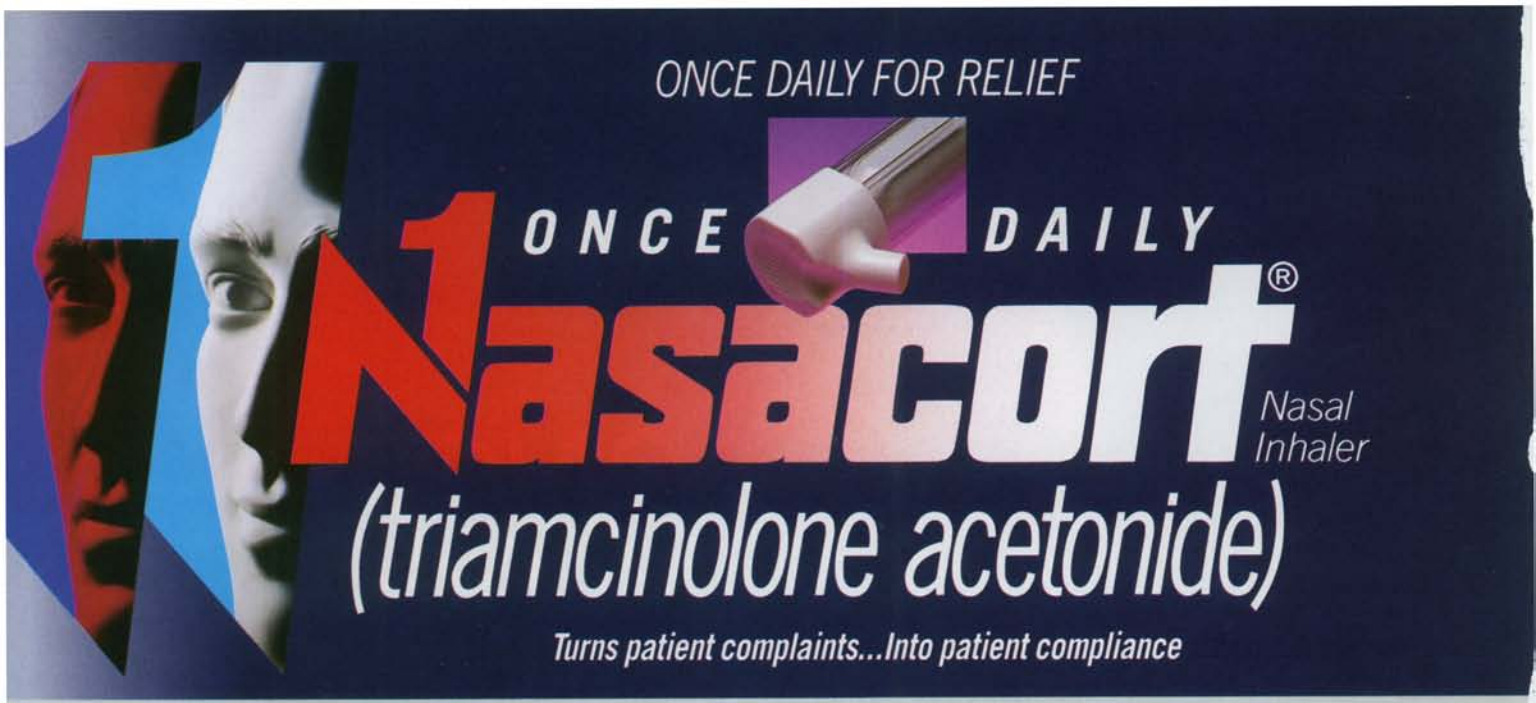
ONCE DAILY

Nasacort® Nasal Inhaler

(triamcinolone acetonide)

Turns patient complaints...Into patient compliance

Please see brief summary of prescribing information on adjacent page.



ONCE DAILY
Nasacort® Nasal Inhaler
(triamcinolone acetonide)

For Intranasal Use Only
Shake Well Before Using

BRIEF SUMMARY

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

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

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

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

PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Please see product circular for full prescribing information.

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

Marketed by:

RHÔNE-POULENC RORER

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

NA06X193(X)A 1/93 FC#93-F18

MIGRAINE PAIN
MIGRAINE PAIN
MIGRAINE PAIN

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.

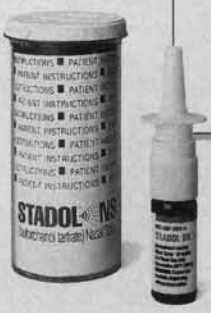
Please see brief summary of prescribing information on following page.

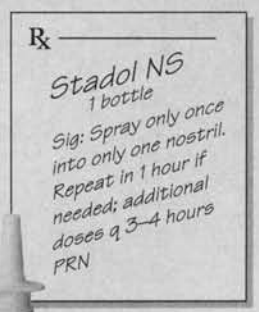
Mead Johnson LABORATORIES
A Bristol-Myers Squibb Company
Princeton, New Jersey 08543
U.S.A.

Dedicated to Excellence in Women's Health Care

STADOL® NS™
(butorphanol tartrate) Nasal Spray

Acute Pain Relief, Delivered in Minutes





Brief Summary

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Pregnancy
Pregnancy Category C

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

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

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

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

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

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

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

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

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

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

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

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

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

CARDIOVASCULAR: VASODILATION*, PALPITATIONS

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

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

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

SKIN AND APPENDAGES: sweating/clammy*, pruritus

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

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

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

CARDIOVASCULAR: hypotension

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

SKIN AND APPENDAGES: rash/hives

UROGENITAL: impaired urination

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

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

BODY AS A WHOLE: edema

CARDIOVASCULAR: hypertension

NERVOUS: *convulsion, delusions*, depression

RESPIRATORY: *apnea*, shallow breathing

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CAUTION: Federal law prohibits dispensing without prescription.

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

A4-K004-4-93

NEW LOW-DOSE

LOZOL® 1.25 MG

INDAPAMIDE TABLETS

A LITTLE MEANS A LOT

TO THE OLDER PATIENT WITH MILD TO MODERATE HYPERTENSION

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

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

Less patient discontinuation than with placebo

Side-effect profile compatible with other antihypertensive agents

Please see brief summary of prescribing information on this page.

LOZOL® (indapamide) 1.25 mg and 2.5 mg tablets
BRIEF SUMMARY

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

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

WARNINGS: Infrequent cases of severe hyponatremia, accompanied by hypokalemia, have been reported with 2.5 mg and 5.0 mg indapamide primarily in elderly females. Symptoms were reversed by electrolyte replenishment. Hyponatremia considered possibly clinically significant (<125 mEq/L) has not been observed in clinical trials with the 1.25 mg dosage (see PRECAUTIONS). Hypokalemia occurs commonly with diuretics (**see ADVERSE REACTIONS, hypokalemia**), and electrolyte monitoring is essential. In general, diuretics should not be given with lithium.

PRECAUTIONS: Perform serum electrolyte determinations at appropriate intervals, especially in patients who are vomiting excessively or receiving parenteral fluids, in patients subject to electrolyte imbalance, or in patients on a salt-restricted diet. In addition, patients should be observed for clinical signs of fluid or electrolyte imbalance, such as hyponatremia, hypochloremic alkalosis, or hypokalemia. The risk of hypokalemia secondary to diuresis and natriuresis is increased with larger doses, with brisk diuresis, with severe cirrhosis, and with concomitant use of corticosteroids or ACTH. Interference with adequate oral intake of electrolytes will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis, such as increased ventricular irritability.

Dilutional hyponatremia may occur in edematous patients; appropriate treatment is usually water restriction. In actual salt depletion, appropriate replacement is the treatment of choice. Chloride deficit is usually mild, not requiring specific treatment except in extraordinary circumstances (liver, renal disease).

Hyperuricemia may occur, and frank gout may be precipitated in certain patients receiving indapamide. Serum concentrations of uric acid should be monitored periodically.

Use with caution in patients with severe renal disease; consider withholding or discontinuing if progressive renal impairment is observed. Renal function tests should be performed periodically.

Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Latent diabetes may become manifest and insulin requirements in diabetic patients may be altered during thiazide administration. A mean increase in glucose of 6.47 mg/dL was observed in patients treated with indapamide 1.25 mg, which was not considered clinically significant in these trials. Serum concentrations of glucose should be monitored routinely during treatment with indapamide.

Calcium excretion is decreased by diuretics pharmacologically related to indapamide. After six to eight weeks of indapamide 1.25 mg treatment and in long-term studies of hypertensive patients with higher doses of indapamide, however, serum concentrations of calcium increased only slightly with indapamide. Indapamide may decrease serum PBI levels without signs of thyroid disturbance. Complications of hyperparathyroidism have not been seen. Discontinue before tests of parathyroid function are performed.

Thiazides have exacerbated or activated systemic lupus erythematosus. Consider this possibility with indapamide.

DRUG INTERACTIONS: LOZOL may add to or potentiate the action of other antihypertensive drugs. The antihypertensive effect of the drug may be enhanced in the postsympathectomized patient. Indapamide may decrease arterial responsiveness to norepinephrine, but this does not preclude the use of norepinephrine.

In mouse and rat lifetime carcinogenicity studies, there were no significant differences in the incidence of tumors between the indapamide-treated animals and the control groups.

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

ADVERSE REACTIONS: Most adverse effects have been mild and transient. From Phase II/III placebo-controlled studies with indapamide 1.25 mg, adverse reactions with ≥5% cumulative incidence: headache, infection, pain, back pain, dizziness, rhinitis; <5% cumulative incidence: asthenia, flu syndrome, abdominal pain, chest pain, constipation, diarrhea, dyspepsia, nausea, peripheral edema, nervousness, hypertonia, cough, pharyngitis, sinusitis, conjunctivitis. All other clinical adverse reactions occurred at an incidence of <1%. In controlled clinical trials of six to eight weeks in duration, 20% of patients receiving indapamide 1.25 mg, 61% of patients receiving indapamide 5.0 mg, and 80% of patients receiving indapamide 10.0 mg had at least one potassium value below 3.4 mEq/L. In the indapamide 1.25 mg group, about 40% of those patients who reported hypokalemia as a laboratory adverse event returned to normal serum potassium values without intervention. Hypokalemia with concomitant clinical signs or symptoms occurred in 2% of patients receiving indapamide 1.25 mg. From Phase II placebo-controlled studies and long-term controlled clinical trials with LOZOL 2.5 mg or 5.0 mg, adverse reactions with ≥ 5% cumulative incidence: headache, dizziness, fatigue, weakness; loss of energy, lethargy, tiredness or malaise, muscle cramps or spasm or numbness of the extremities, nervousness, tension, anxiety, irritability or agitation; <5% cumulative incidence: lightheadedness, drowsiness, vertigo, insomnia, depression, blurred vision, constipation, nausea, vomiting, diarrhea, gastric irritation, abdominal pain or cramps, anorexia, orthostatic hypotension, premature ventricular contractions, irregular heart beat, palpitations, frequency of urination, nocturia, polyuria, rash, hives, pruritus, vasculitis, impotence or reduced libido, rhinorrhea, flushing, hyperuricemia, hyperglycemia, hyponatremia, hypochloremia, increase in serum BUN or creatinine, glycosuria, weight loss, dry mouth, tingling of extremities. Hypokalemia with concomitant clinical signs or symptoms occurred in 3% of patients receiving indapamide 2.5 mg q.d. and 7% of patients receiving indapamide 5 mg q.d. In long-term controlled clinical trials comparing the hypokalemic effects of daily doses of indapamide and hydrochlorothiazide, however, 47% of patients receiving indapamide 2.5 mg, 72% of patients receiving indapamide 5 mg, and 44% of patients receiving hydrochlorothiazide 50 mg had at least one potassium value (out of a total of 11 taken during the study) below 3.5 mEq/L. In the indapamide 2.5 mg group, over 50% of those patients returned to normal serum potassium values without intervention. Other adverse reactions reported with antihypertensive/diuretics are intrahepatic cholestatic jaundice, sialadenitis, xanthopsia, photosensitivity, purpura, bullous eruptions, Stevens-Johnson syndrome, necrotizing angiitis, fever, respiratory distress (including pneumonitis), anaphylactic reactions, agranulocytosis, leukopenia, thrombocytopenia, aplastic anemia.

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.
Keep tightly closed. Store at controlled room temperature, 15°-30°C (59°-86°F). Avoid excessive heat. Dispense in tight containers as defined in USP.
See product circular for full prescribing information.
Revised: April 1993

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

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

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

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

RHÔNE-POULENC RORER

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

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

LODINE® (etodolac) **CAPSULES**

BRIEF SUMMARY

Indications and Usage: Lodine 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. Patients in whom Lodine, aspirin, or other NSAIDs induce asthma, rhinitis, urticaria, or other allergic reactions. Fatal asthmatic reactions have been reported in such patients receiving NSAIDs. **Warnings:** Serious GI toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAIDs. Remain alert for ulceration and bleeding in such patients even in the absence of previous GI-tract symptoms. In clinical trials, symptomatic upper GI ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3-6 months and in about 2-4% of patients treated for 1 year. Inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur. Studies have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than others and most spontaneous reports of fatal GI events are in this population. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity. **Precautions:** Patients with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly are at greater risk of overt renal decompensation. If this occurs, discontinue the drug. With NSAIDs, borderline elevations of liver tests may occur in up to 15% of patients. They may disappear, remain unchanged, or progress with continued therapy. Elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for the development of a more severe hepatic reaction. Although such reactions are rare, if abnormal liver tests persist or worsen, if liver disease develops or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue therapy. Anemia is sometimes seen, which may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis. Patients should have their hemoglobin or hematocrit checked if they develop signs or symptoms of anemia. 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:** NSAID side effects can cause discomfort and, rarely, may be serious, such as GI bleeding that may result in hospitalization and even fatal outcomes. Physicians may wish to discuss with patients the potential risks and likely benefits of Lodine treatment, particularly when it may be used for less serious conditions in which treatment without Lodine may be an acceptable alternative. **Laboratory Tests:** Because serious GI-tract ulceration and bleeding can occur without warning symptoms, follow chronically treated patients for signs and symptoms of these and inform them of the importance of this follow-up. **Drug Interactions:** Use caution when giving concomitantly with antacids, aspirin, warfarin, phenytoin, glyburide, diuretics, cyclosporine, digoxin, lithium, or methotrexate. Coadministration of Lodine and phenylbutazone not recommended. **Drug/Laboratory Test Interactions:** False-positive for urinary bilirubin and/or urinary ketone. **Teratogenic Effects: Pregnancy Category C:** Lodine should be used during pregnancy only if the potential benefits justify the potential risk to the fetus. Avoid use during late pregnancy. **Labor and Delivery:** Lodine is not recommended. **Nursing Mothers:** Safety has not been established. Caution should be exercised if Lodine is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in children have not been established. **Geriatric Population:** No dosage adjustment is generally necessary, nevertheless caution should be exercised. **Adverse Reactions: Incidence greater than or equal to 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. Drug-related patient complaints occurring in fewer than 3%, but more than 1%, are unmarked. **Incidence less than 1% — probably causally related:** (Reactions not seen in clinical trials are 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, *cholestatic hepatitis*, hepatitis, *cholestatic jaundice, jaundice*, PUB (i.e., peptic ulcer with or without bleeding and/or perforation), *pancreatitis*. Hemic and lymphatic system: ecchymosis, anemia, thrombocytopenia, bleeding time increased, *agranulocytosis, hemolytic anemia, neutropenia, pancytopenia*. Metabolic and nutritional: edema, serum creatinine increase, *hyperglycemia in previously controlled diabetic patients*. Nervous system: insomnia, somnolence. Respiratory system: asthma. Skin and appendages: angioedema, sweating, urticaria; vesiculobullous rash, *cutaneous vasculitis with purpura, Stevens-Johnson Syndrome*, hyperpigmentation, *erythema multiforme*. Special senses: photophobia, transient visual disturbances. Urogenital system: *elevated BUN, renal failure, renal insufficiency, renal papillary necrosis*. **Incidence less than 1% — causal relationship unknown:** 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 has no addiction potential in humans. **Overdosage:** May develop lethargy, drowsiness, nausea, vomiting, epigastric pain, GI bleeding, coma, or anaphylactoid reaction. Hypertension, acute renal failure, and respiratory depression are rare. Empty stomach and use usual supportive measures. **See package insert for full prescribing information.**

Ayerst Laboratories Inc.
A Wyeth-Ayerst Company
Philadelphia, PA 19101

CI 4000-5

November 10, 1992

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

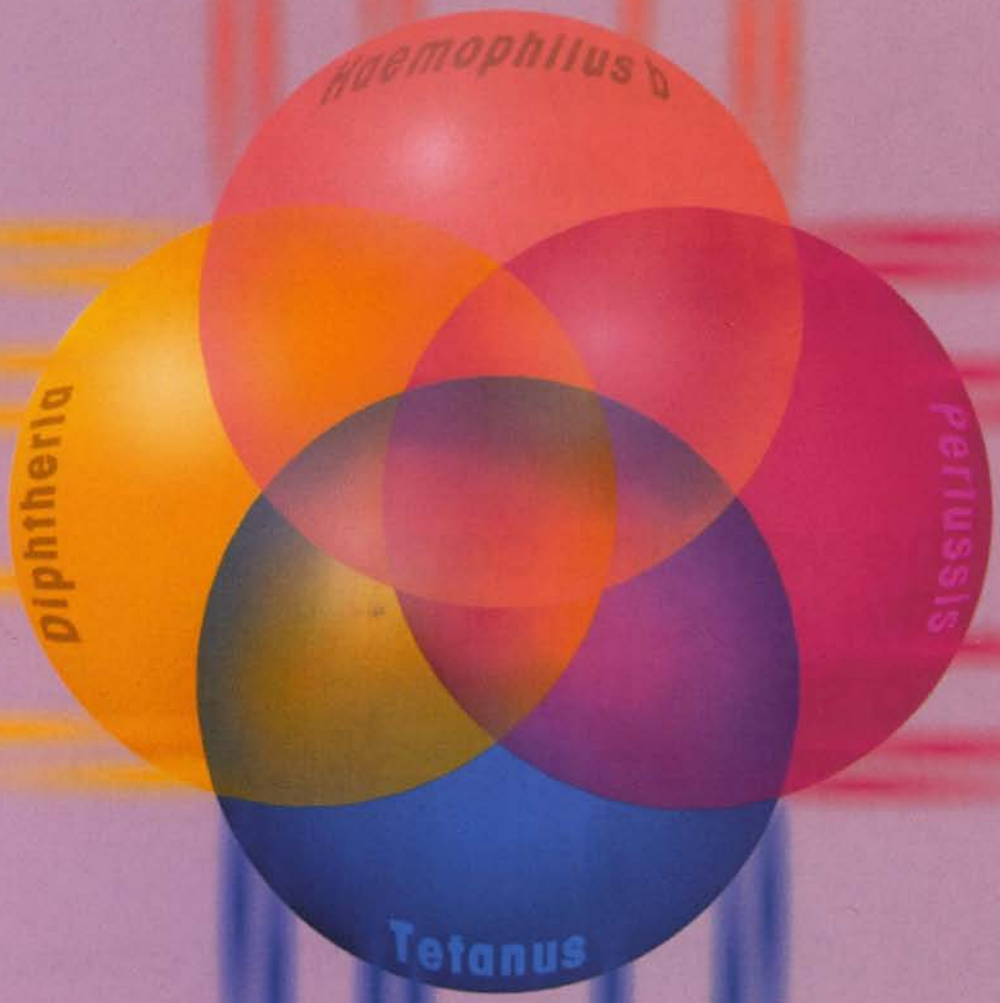
*Safety in children has not been established. In patients 65 years and older, no substantial differences in the pharmacokinetics or side-effects profile of LODINE were seen compared with the general population.

†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.

Now, protect against four...



With one exciting new combination vaccine

Introducing **TETRAMUNE**™

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed and Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate)

From Lederle-Praxis Biologicals

New from
Lederle-Praxis Biologicals

TETRAMUNE™

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed and Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate)

The vaccine components of HibTITER®/HbOC* and TRI-IMMUNOL®/DTP† in a single 0.5 mL injection — *requires no reconstitution*

Safety clinically proven in 6,793 US children[1]

- Overall safety profile of TETRAMUNE comparable to that of HibTITER/HbOC and TRI-IMMUNOL/DTP administered separately[1]:
  - — At 2, 4, and 6 months of age
  - — At 15 to 21 months of age‡
- No significant differences in rare adverse events as observed in hospitalization or emergency room visits[1]

*Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate). Manufactured by Praxis Biologics, Inc.

†Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed. Manufactured by Lederle Laboratories.

‡In toddlers who had received three primary doses of DTP and no HbOC as infants.

§Higher antibody titers cannot be directly translated to mean higher efficacy.

//Antibodies to: *Haemophilus* b (≥1.0 mg/mL), diphtheria toxoid (≥0.01 IU/mL), tetanus toxoid (≥0.01 EU/mU), pertussis agglutinogens (≥16 reciprocal dilution).

References: 1. Data on file. Lederle Laboratories and Praxis Biologics, Inc., NY. **2.** Paradiso P, Hogerman D, Madore D, et al. Safety and immunogenicity in infants of a tetravalent vaccine composed of HbOC (HibTITER®) and DTP (TRI-IMMUNOL®). *Pediatr Res*. 1992;31(4, pt 2):Abstract #1028.

As immunogenic as HibTITER/HbOC and TRI-IMMUNOL/DTP administered separately[1,2]

- Equivalent or higher antibody responses following three primary doses at 2, 4, and 6 months of age[1,2] or a single dose at 15 to 21 months of age[1‡§]
- Equivalent percentage of children attaining specific antibody levels[1//]

Please consult brief summary of full Prescribing Information on adjacent page.

New from
Lederle-Praxis Biologicals

TETRAMUNE™

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed and Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate)

Combined protection in a single 0.5 mL injection

Recommended immunization schedule* for TETRAMUNE	
Infant series	2, 4, and 6 months
Fourth dose HibTITER®/HbOC† and ACEL-IMUNE®/DTaP‡ may be administered separately as an alternative to TETRAMUNE at 15 to 18 months and 17 to 24 months§ of age, respectively	15 months

To complete the recommended 5-dose DTP immunization series, you may use ACEL-IMUNE/DTaP or TRI-IMMUNOL®/DTP// at 4 to 6 years of age

Interchanging Haemophilus *b conjugate vaccines in infants is not recommended. However, TETRAMUNE may be administered following separate immunizations with DTP vaccine and HibTITER/HbOC.**

- To order convenient, ready-to-use, 10-dose vials, call 1-800-L-E-D-E-R-L-E (533-3753) or contact your local Lederle Medical Representative.

*Please refer to brief summary of full Prescribing Information for complete immunization schedule for TETRAMUNE.

†Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate). Manufactured by Praxis Biologics, Inc.

‡Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed. ACEL-IMUNE manufactured by Lederle Laboratories. Acellular pertussis component manufactured by Takeda Chemical Industries, Ltd.

§ACEL-IMUNE may be considered for immunization at 15 months when it is expected that the child may not return at 18 months for immunization.

//Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed. Manufactured by Lederle Laboratories.

Please consult brief summary of full Prescribing Information on adjacent page.

TETRAMUNE™

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed and Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate)

Brief Summary

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed and Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate) TETRAMUNE™

For complete Prescribing Information and references, please consult package insert.

INDICATIONS AND USAGE

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed and Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate) TETRAMUNE, is indicated for the active immunization of children 2 months of age to 5 years of age for protection against diphtheria, tetanus, pertussis, and Haemophilus b disease when indications for immunization with DTP vaccine and Haemophilus b Conjugate Vaccine coincide. Typically, this is at 2, 4, 6, and 15 months of age.

As with any vaccine, TETRAMUNE may not protect 100% of individuals receiving the vaccine.

CONTRAINDICATIONS

HYPERSENSITIVITY TO ANY COMPONENT OF THE VACCINE, INCLUDING THIMEROSAL, A MERCURY DERIVATIVE, IS A CONTRAINDICATION.

IMMUNIZATION SHOULD BE DEFERRED DURING THE COURSE OF ANY FEBRILE ILLNESS OR ACUTE INFECTION. THE IMMUNIZATION PRACTICES ADVISORY COMMITTEE (ACIP) HAS STATED THAT "...MINOR ILLNESSES SUCH AS MILD UPPER RESPIRATORY INFECTIONS WITH OR WITHOUT LOW GRADE FEVER ARE NOT CONTRAINDICATIONS."

IMMUNIZATION WITH TETRAMUNE IS CONTRAINDICATED IF THE CHILD HAS EXPERIENCED ANY EVENT FOLLOWING PREVIOUS IMMUNIZATION WITH A PERTUSSIS-CONTAINING VACCINE, WHICH IS CONSIDERED BY THE AAP OR ACIP TO BE A CONTRAINDICATION TO FURTHER DOSES OF PERTUSSIS VACCINE. THESE EVENTS INCLUDE:

AN IMMEDIATE ANAPHYLACTIC REACTION.

ENCEPHALOPATHY OCCURRING WITHIN 7 DAYS FOLLOWING VACCINATION. THIS IS DEFINED AS AN ACUTE, SEVERE CENTRAL-NERVOUS-SYSTEM DISORDER OCCURRING WITHIN 7 DAYS FOLLOWING VACCINATION, AND GENERALLY CONSISTING OF MAJOR ALTERATIONS IN CONSCIOUSNESS, UNRESPONSIVENESS, GENERALIZED OR FOCAL SEIZURES THAT PERSIST MORE THAN A FEW HOURS, WITH FAILURE TO RECOVER WITHIN 24 HOURS.

THE OCCURRENCE OF ANY TYPE OF NEUROLOGICAL SYMPTOMS OR SIGNS, INCLUDING ONE OR MORE CONVULSIONS (SEIZURES) FOLLOWING ADMINISTRATION OF TETRAMUNE IS GENERALLY A CONTRAINDICATION TO FURTHER USE. ANY DECISION TO ADMINISTER SUBSEQUENT DOSES OF A VACCINE CONTAINING DIPHTHERIA, TETANUS, OR PERTUSSIS ANTIGENS SHOULD BE DELAYED UNTIL THE PATIENT'S NEUROLOGICAL STATUS IS BETTER DEFINED.

THE PRESENCE OF ANY EVOLVING OR CHANGING DISORDER AFFECTING THE CENTRAL NERVOUS SYSTEM IS A CONTRAINDICATION TO ADMINISTRATION OF A PERTUSSIS-CONTAINING VACCINE SUCH AS TETRAMUNE REGARDLESS OF WHETHER THE SUSPECTED NEUROLOGICAL DISORDER IS ASSOCIATED WITH OCCURRENCE OF SEIZURE ACTIVITY OF ANY TYPE.

STUDIES HAVE INDICATED THAT A PERSONAL OR FAMILY HISTORY OF SEIZURES IS ASSOCIATED WITH INCREASED FREQUENCY OF SEIZURES FOLLOWING PERTUSSIS IMMUNIZATION.

The ACIP and the AAP recognize certain circumstances in which children with stable central nervous system disorders, including well-controlled seizures or satisfactorily explained single seizures, may receive pertussis vaccine. The ACIP and AAP do not consider a family history of seizures to be a contraindication to pertussis vaccine despite the increased risk of seizures in these individuals.

The decision to administer a pertussis-containing vaccine to children must be made by the physician on an individual basis, with consideration of all relevant factors, and assessment of potential risks and benefits for that individual. The physician should review the full text of ACIP and AAP guidelines prior to considering vaccination for children. The parent or guardian should be advised of the increased risk involved.

There are no data on whether the prophylactic use of antipyretics can decrease the risk of febrile convulsions. However, data suggest that acetaminophen will reduce the incidence of postvaccination fever. The ACIP and AAP suggest administering acetaminophen at age-appropriate doses at the time of vaccination and every 4 to 6 hours to children at higher risk for seizures than the general population.

ROUTINE IMMUNIZATION SHOULD BE DEFERRED DURING AN OUTBREAK OF POLIOMYELITIS PROVIDING THE PATIENT HAS NOT SUSTAINED AN INJURY THAT INCREASES THE RISK OF TETANUS AND PROVIDING AN OUTBREAK OF DIPHTHERIA OR PERTUSSIS DOES NOT OCCUR SIMULTANEOUSLY.

The clinical judgment of the attending physician should prevail at all times.

WARNINGS

THE ACIP STATES THAT IF ANY OF THE FOLLOWING EVENTS OCCUR IN TEMPORAL RELATION TO RECEIPT OF DTP, THE DECISION TO GIVE SUBSEQUENT DOSES OF VACCINE CONTAINING THE PERTUSSIS COMPONENT SHOULD BE CAREFULLY CONSIDERED.

TEMPERATURE OF ≥40.5°C (105°F) WITHIN 48 HOURS NOT DUE TO IDENTIFIABLE CAUSE.

COLLAPSE OR SHOCK-LIKE STATE (HYPOTONIC-HYPORESPONSIVE EPISODE) WITHIN 48 HOURS.

PERSISTENT, INCONSOLABLE CRYING LASTING ≥3 HOURS, OCCURRING WITHIN 48 HOURS.

CONVULSIONS WITH OR WITHOUT FEVER OCCURRING WITHIN 3 DAYS.

"ALTHOUGH THESE EVENTS WERE CONSIDERED ABSOLUTE CONTRAINDICATIONS IN PREVIOUS ACIP RECOMMENDATIONS, THERE MAY BE CIRCUMSTANCES, SUCH AS A HIGH INCIDENCE OF PERTUSSIS, IN WHICH THE POTENTIAL BENEFITS OUTWEIGH POSSIBLE RISKS, PARTICULARLY BECAUSE THESE EVENTS ARE NOT ASSOCIATED WITH PERMANENT SEQUELAE."

IF A CONTRAINDICATION TO ANY OF THE COMPONENTS OF THIS COMBINATION VACCINE EXISTS (SEE **CONTRAINDICATIONS** SECTION), THEN TETRAMUNE SHOULD NOT BE USED. FOR EXAMPLE, IF THERE IS A CONTRAINDICATION AGAINST THE USE OF A PERTUSSIS VACCINE COMPONENT, THEN DIPHTHERIA AND TETANUS TOXOIDS ADSORBED, FOR PEDIATRIC USE (DT), AND HAEMOPHILUS b CONJUGATE VACCINE (DIPHTHERIA CRM_{197} PROTEIN CONJUGATE) HibTITER®, AS SEPARATE INJECTIONS, SHOULD BE SUBSTITUTED FOR EACH OF THE REMAINING DOSES.

THE OCCURRENCE OF SUDDEN INFANT DEATH SYNDROME (SIDS) HAS BEEN REPORTED FOLLOWING ADMINISTRATION OF DTP. HOWEVER, A LARGE CASE-CONTROL STUDY IN THE US REVEALED NO CAUSAL RELATIONSHIP BETWEEN RECEIPT OF DTP VACCINE AND SIDS. A RECENT STUDY OF 6,497 INFANTS IN NORTHERN CALIFORNIA FOUND NO INCREASE IN THE RATE OF SIDS AMONG TETRAMUNE RECIPIENTS.

AS WITH ANY INTRAMUSCULAR INJECTION, TETRAMUNE SHOULD BE GIVEN WITH CAUTION TO INFANTS OR CHILDREN WITH THROMBOCYTOPENIA OR ANY COAGULATION DISORDER THAT WOULD CONTRAINDICATE INTRAMUSCULAR INJECTION (SEE **DRUG INTERACTIONS**).

As reported with Haemophilus b polysaccharide vaccine, cases of Haemophilus type b disease may occur prior to the onset of the protective effect of this vaccine.

TETRAMUNE WILL NOT PROTECT AGAINST *H. INFLUENZAE* OTHER THAN TYPE b STRAINS.

ANTIGENURIA HAS BEEN DETECTED FOLLOWING RECEIPT OF HAEMOPHILUS b CONJUGATE VACCINE AND THEREFORE ANTIGEN DETECTION IN URINE MAY NOT HAVE DIAGNOSTIC VALUE IN SUSPECTED HAEMOPHILUS b DISEASE WITHIN 2 WEEKS OF IMMUNIZATION.

PRECAUTIONS

General: CARE IS TO BE TAKEN BY THE HEALTH CARE PROVIDER FOR SAFE AND EFFECTIVE USE OF THIS PRODUCT.

1. TETRAMUNE is not routinely recommended for immunization of persons older than 5 years of age. Under certain circumstances, TETRAMUNE may be used beyond age 5 years. Because TETRAMUNE contains pediatric DTP vaccine, it is not recommended for use beyond the seventh birthday.
2. PRIOR TO ADMINISTRATION OF ANY DOSE OF TETRAMUNE, THE PARENT OR GUARDIAN SHOULD BE ASKED ABOUT THE PERSONAL HISTORY, FAMILY HISTORY, AND RECENT HEALTH STATUS. THE HEALTH CARE PROVIDER SHOULD ASCERTAIN PREVIOUS IMMUNIZATION HISTORY, CURRENT HEALTH STATUS, AND OCCURRENCE OF ANY SYMPTOMS AND/OR SIGNS OF AN ADVERSE EVENT AFTER PREVIOUS IMMUNIZATIONS, IN THE CHILD TO BE IMMUNIZED, IN ORDER TO DETERMINE THE EXISTENCE OF ANY CONTRAINDICATION TO IMMUNIZATION WITH TETRAMUNE AND TO ALLOW AN ASSESSMENT OF BENEFITS AND RISKS.
3. BEFORE THE INJECTION OF ANY BIOLOGICAL, THE HEALTH CARE PROVIDER SHOULD TAKE ALL PRECAUTIONS KNOWN FOR THE PREVENTION OF ALLERGIC OR ANY OTHER SIDE REACTIONS. This should include: a review of the patient's history regarding possible sensitivity; the ready availability of epinephrine 1:1000 and other appropriate agents used for control of immediate allergic reactions; and a knowledge of the recent literature pertaining to use of the biological concerned, including the nature of side effects and adverse reactions that may follow its use.
4. Children with impaired immune responsiveness, whether due to the use of immunosuppressive therapy (including irradiation, corticosteroids, antimetabolites, alkylating agents, and cytotoxic agents), a genetic defect, human immunodeficiency virus (HIV) infection, or other causes, may have reduced antibody response to active immunization procedures. Deferral of administration of vaccine may be considered in individuals receiving immunosuppressive therapy. Other groups should receive this vaccine according to the usual recommended schedule. (See **DRUG INTERACTIONS**.)
5. This product is not contraindicated based on the presence of human immunodeficiency virus infection.
6. *Since this product is a suspension containing an adjuvant, shake vigorously to obtain a uniform suspension prior to withdrawing each dose from the multiple dose vial.*
7. A separate sterile syringe and needle or a sterile disposable unit should be used for each individual patient to prevent transmission of infectious agents from one person to another. Needles should be disposed of properly and should not be recapped.
8. Special care should be taken to prevent injection into a blood vessel.

National Childhood Vaccine Injury Act: This Act requires that the manufacturer and lot number of the vaccine administered be recorded by the health care provider in the vaccine recipient's permanent medical record (or in a permanent office log or file), along with the date of administration of the vaccine and the name, address, and title of the person administering the vaccine.

The Act further requires the health care provider to report to the Secretary of the Department of Health and Human Services through the Vaccine Adverse Event Reporting System (VAERS) the occurrence following immunization of any event set forth in the Vaccine Injury Table, including: anaphylaxis or anaphylactic shock within 24 hours; encephalopathy or encephalitis within 7 days; shock-collapse or hypotonic-hyporesponsive collapse within 7 days; residual seizure disorder; any acute complication or sequelae (including death) of above events, or any event that would contraindicate further doses of vaccine, according to the package insert for TETRAMUNE.

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed and Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate) TETRAMUNE™

The US Department of Health and Human Services has established VAERS to accept all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events required by the National Childhood Vaccine Injury Act of 1986. The VAERS toll-free number for VAERS forms and information is 800-822-7967.

Information for Patient: PRIOR TO ADMINISTRATION OF TETRAMUNE, HEALTH CARE PERSONNEL SHOULD INFORM THE PARENT, GUARDIAN, OR OTHER RESPONSIBLE ADULT OF THE RECOMMENDED IMMUNIZATION SCHEDULE FOR PROTECTION AGAINST DIPHTHERIA, TETANUS, PERTUSSIS, AND HAEMOPHILUS b DISEASE AND THE BENEFITS AND RISKS TO THE CHILD RECEIVING THIS VACCINE. GUIDANCE SHOULD BE PROVIDED ON MEASURES TO BE TAKEN SHOULD ADVERSE EVENTS OCCUR, SUCH AS ANTIPYRETIC MEASURES FOR ELEVATED TEMPERATURES AND THE NEED TO REPORT ADVERSE EVENTS TO THE HEALTH CARE PROVIDER. PARENTS SHOULD BE PROVIDED WITH VACCINE INFORMATION PAMPHLETS AT THE TIME OF EACH VACCINATION, AS STATED IN THE NATIONAL CHILDHOOD VACCINE INJURY ACT.

THE HEALTH CARE PROVIDER SHOULD INFORM THE PATIENT, PARENT, OR GUARDIAN OF THE IMPORTANCE OF COMPLETING THE IMMUNIZATION SERIES.

PATIENTS, PARENTS, OR GUARDIANS SHOULD BE INSTRUCTED TO REPORT ANY SERIOUS ADVERSE REACTIONS TO THEIR HEALTH CARE PROVIDER.

Drug Interactions: Children receiving immunosuppressive therapy may have a reduced response to active immunization procedures.

As with other intramuscular injections, TETRAMUNE should be given with caution to children on anticoagulant therapy.

Tetanus Immune Globulin or Diphtheria Antitoxin, if used, should be given in a separate site with a separate needle and syringe.

The AAP recommends that influenza virus vaccine should not be administered within 3 days of immunization with a pertussis-containing vaccine since both vaccines may cause febrile reactions in young children.

Data are not yet available concerning adverse reactions that may occur when TETRAMUNE is given simultaneously with Oral Poliovirus Vaccine (OPV), Measles-Mumps-Rubella (MMR) or Hepatitis B (HB) vaccine at separate sites. Also, data are not available concerning the effects on immune response of OPV, MMR or HB vaccine when TETRAMUNE is given simultaneously. Clinical studies with TETRAMUNE did however allow for the administration of OPV according to the routine immunization schedule for OPV.

Carcinogenesis, Mutagenesis, Impairment of Fertility: TETRAMUNE has not been evaluated for its carcinogenic, mutagenic potential or for impairment of fertility.

Pregnancy: *Pregnancy Category C:* Animal reproduction studies have not been conducted with TETRAMUNE. This product is not recommended for use in individuals 7 years of age or older.

Pediatric Use: The safety and effectiveness of TETRAMUNE in children below the age of 6 weeks have not been established.

For immunization of children 7 years of age or older, Tetanus and Diphtheria Toxoids Adsorbed for Adult Use (Td) is recommended. If contraindication to the pertussis component exists, Diphtheria and Tetanus Toxoids Adsorbed, for Pediatric Use (DT) should be substituted in children who have not reached their seventh birthday.

Full protection against the indicated diseases (tetanus, diphtheria, pertussis, and Haemophilus type b disease) is based on a full course of immunization.

ADVERSE REACTIONS

The safety of TETRAMUNE has been evaluated in 6,793 children at 2, 4, and 6 months of age or at 15 to 18 months of age in three separate sites. The percent of doses administered associated with injection site reactions within 72 hours, or common systemic symptoms within 4 days, is summarized below:

	% of Doses Associated with Symptoms		
	Infants‡ (542 doses)	Infants§ (7269 doses)	Toddlers (107 doses)
Local*			
Erythema	34	19	40
Pain/Tenderness	21	30	65
Swelling	20	20	43
Warmth	16	–	35
Systemic†			
Fever ≥38.0°C	24	40 ‖	33
Irritability	42	54	49
Drowsiness	26	–	9
Restless sleep	–	28	–
Loss of appetite	–	4	–
Vomiting	5	2	1
Diarrhea	9	1	10
Rash	3	–	0

* within 72 hours of immunization

† within 4 days of immunization

‡ a separate multicenter safety and immunogenicity study, not a subset of the 7269 infant Kaiser study

§ data for this study all collected within 24 hours of immunization (percentages calculated from a range of 7269 to 7500 doses) in the Kaiser Permanente Safety and Immunogenicity Study

‖ perceived fever

Based on review of the Kaiser-Permanente Medical Care Program utilization data base of hospitalizations (within 60 days) and emergency room visits (within 30 days of immunization) in 6,497 infants who received TETRAMUNE, the most common reasons for seeking care include: trauma, viral illness, and respiratory illnesses (eg, upper respiratory infection, otitis media, bronchitis/bronchiolitis, and pneumonia). One child who received TETRAMUNE became transiently pale and tremulous without loss of responsiveness 4 hours after immunization and was hospitalized with a diagnosis of seizure. No other hospital visits for seizure or hypotonic, hyporesponsive episodes were reported within 72 hours of immunization. These results were not different from those observed in 3,935 infants who received DTP and HbOC at separate injection sites.

As with other aluminum-containing vaccines, a nodule may occasionally be palpable at the injection site for several weeks. Although not seen in studies with TETRAMUNE, sterile abscess formation or subcutaneous atrophy at the injection site may also occur.

The following significant adverse events have occurred following administration of DTP vaccines: persistent, inconsolable crying ≥3 hours (1/100 doses), high-pitched, unusual crying (1/1000 doses), fever ≥40.5°C (105°F) (1/330 doses), transient shock-like (hypotonic, hyporesponsive) episode (1/1750 doses), convulsions (1/1750 doses).

The ACIP states: "Although DTP may rarely produce symptoms that some have classified as acute encephalopathy, a causal relation between DTP vaccine and permanent brain damage has not been demonstrated. If the vaccine ever causes brain damage, the occurrence of such an event must be exceedingly rare. A similar conclusion has been reached by the Committee on Infectious Diseases of the American Academy of Pediatrics, the Child Neurology Society, the Canadian National Advisory Committee on Immunization, the British Joint Committee on Vaccination and Immunization, the British Pediatric Association, and the Institute of Medicine."

The occurrence of sudden infant death syndrome (SIDS) has been reported following administration of DTP. However, a large case-control study in the US revealed no causal relationship between receipt of DTP vaccine and SIDS. A recent study of 6,497 infants in northern California found no increase in the rate of SIDS among TETRAMUNE recipients.

Onset of infantile spasms has occurred in infants who have recently received DTP or DT. Analysis of data from the National Childhood Encephalopathy Study on children with infantile spasms showed that receipt of preparations containing diphtheria, tetanus, and/or pertussis antigens was not causally related to infantile spasms. The incidence of onset of infantile spasms increases at 3 to 9 months of age, the time period in which the second and third doses of DTP are generally given. Therefore, some cases of infantile spasms can be expected to be related by chance alone to recent receipt of vaccines containing DTP.

Bulging fontanel has been reported after DTP immunization, although no cause and effect relationship has been established.

Cardiac effects and respiratory difficulties, including apnea, have been reported rarely following DTP immunization.

Other events that have been reported following administration of vaccines containing diphtheria, tetanus, pertussis, or Haemophilus b antigens include: urticaria, erythema multiforme or other rash, arthralgias, and, more rarely, a severe anaphylactic reaction (eg, urticaria with swelling of the mouth, difficulty breathing, hypotension, or shock) and neurological complications, such as convulsions, encephalopathy, and various mono- and polyneuropathies, including Guillain-Barré syndrome. Permanent neurological disability and death have also been reported rarely in temporal relation to immunization although a causal relationship has not been established.

DOSAGE AND ADMINISTRATION

For Intramuscular Use Only.

See **DOSAGE AND ADMINISTRATION** in full Prescribing Information for complete dosing and precautionary information.

Manufactured by
LEDERLE LABORATORIES
A Division of American Cyanamid Company
Pearl River, NY 10965

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REV 3/93
L-32092-93

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, selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta, selectivity is not absolute, the lowest possible dose of TENORMIN should be used with therapy initiated at 50 mg and a beta,-stimulating agent (bronchodilator) should be made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

	Conventional Therapy Pius 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, stimulant such as isoproterenol or terbutaline and/or aminophylline.

HYPOGLYCEMIA: Intravenous glucose.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

HOW SUPPLIED

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

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

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

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

TENORMIN I.V. Injection

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

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

REV Y 03/92

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Lactofree™	**LACTOSE FREE**	**MILK PROTEIN**	**VEGETABLE OIL BLEND**
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‡ We know of no studies showing clinical benefits from feeding infants formulas with fatty acid profiles similar to breast milk, but Mead Johnson believes it is prudent and appropriate to market formulas with such profiles.
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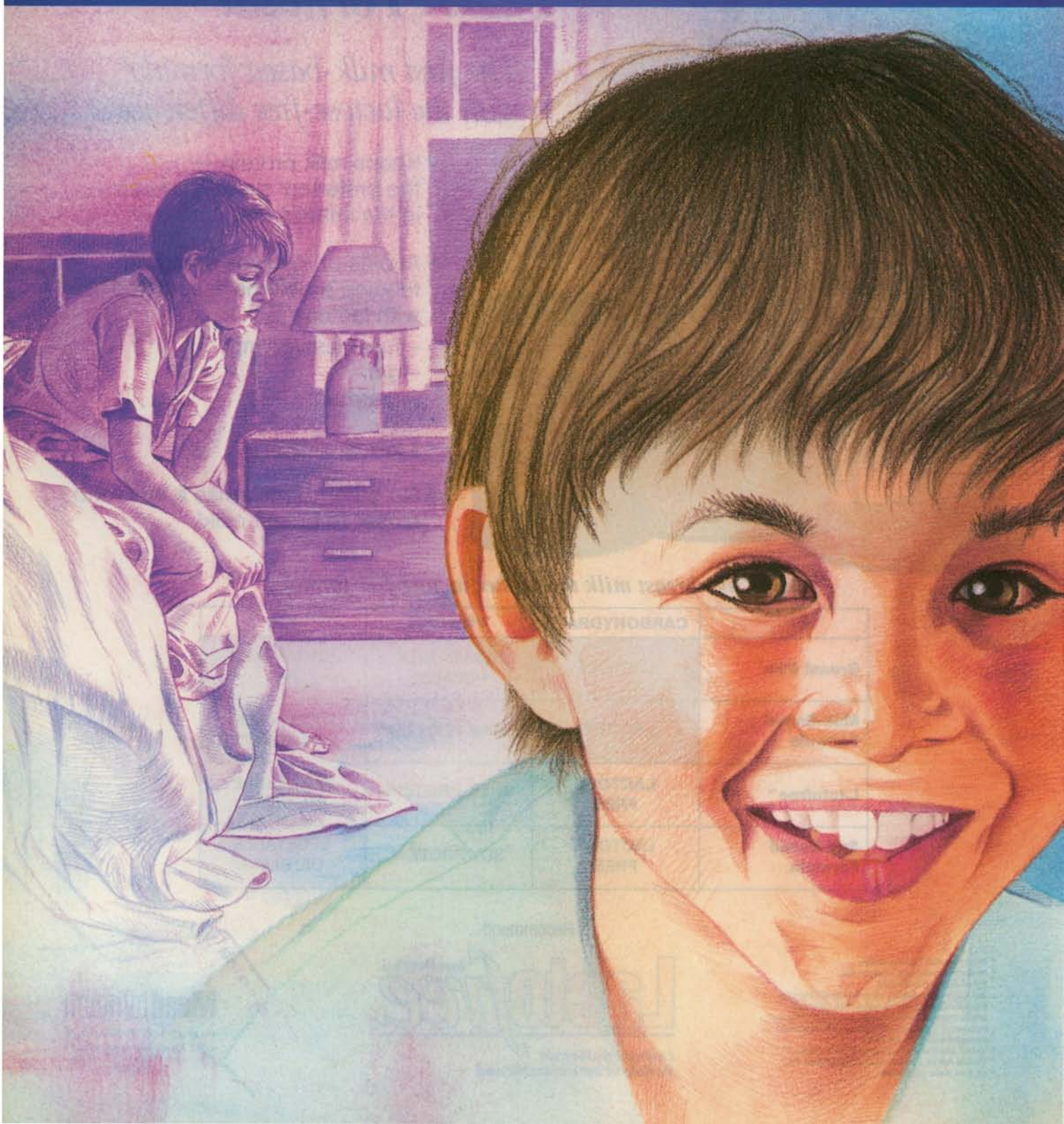
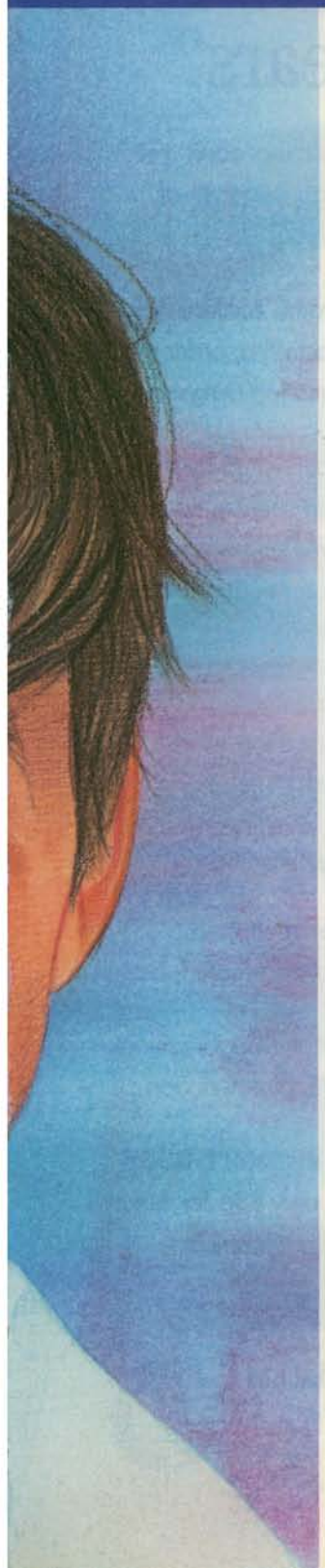


morning after morning



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- Well tolerated…an incidence of adverse events comparable to placebo
- No adverse experiences reported in a study of 28 children, 11 treated for 12 to 42 months[2]
- Approximately 20 years of safe use in children with diabetes insipidus[3]

Works effectively, rapidly

- Success rates as high as 82%[4]
- Significant response in as few as 1-3 days[5]

Works to improve children's self-concept

- Children frequently experience feelings of happiness and achievement at becoming dry[6]
- Significantly improves self-concept, restores quality of life[7]

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

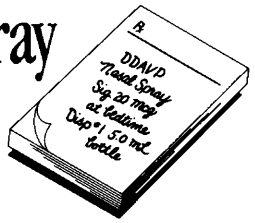
DDAVP® Nasal Spray
(desmopressin acetate) 5mL

Dry Nights For Good Mornings

Please see Brief Summary of prescribing information on following page.

DDAVP® Nasal Spray
(desmopressin acetate) 5mL

Dry Nights For Good Mornings



Brief Summary
CONTRAINDICATION: Known hypersensitivity to DDAVP Nasal Spray.
WARNINGS:
1. For intranasal use only.
2. In very young and elderly patients in particular, fluid intake should be adjusted in order to decrease the potential occurrence of water intoxication and hyponatremia. Particular attention should be paid to the possibility of the rare occurrence of an extreme decrease in plasma osmolality and resulting seizures.

PRECAUTIONS:
General: DDAVP Nasal Spray at high dosage has infrequently produced a slight elevation of blood pressure, which disappeared with a reduction in dosage. The drug should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease because of possible rise in blood pressure.
DDAVP Nasal Spray should be used with caution in patients with conditions associated with fluid and electrolyte imbalance, such as cystic fibrosis, because these patients are prone to hyponatremia.
Central Cranial Diabetes Insipidus: Since DDAVP Nasal Spray is used intranasally, changes in the nasal mucosa such as scarring, edema, or other disease may cause erratic, unreliable absorption in which case DDAVP Nasal Spray should not be used. For such situations, DDAVP injection should be considered.
Primary Nocturnal Enuresis: If changes in the nasal mucosa have occurred, unreliable absorption may result. DDAVP Nasal Spray should be discontinued until the nasal problems resolve.
Information for Patients: Patients should be informed that the bottle accurately delivers 50 doses of 10 mcg each. Any solution remaining after 50 doses should be discarded since the amount delivered thereafter may be substantially less than 10 mcg of drug. No attempt should be made to transfer remaining solution to another bottle. Patients should be instructed to read accompanying directions on use of the spray pump carefully before use.
Laboratory Tests: Laboratory tests for following the patient with central cranial diabetes insipidus or post-surgical or head trauma-related polyuria and polydipsia include urine volume and osmolality. In some cases plasma osmolality may be required. For the healthy patient with primary nocturnal enuresis, serum electrolytes should be checked at least once if therapy is continued beyond 7 days.
Drug Interactions: Although the pressor activity of DDAVP Nasal Spray is very low compared to the antidiuretic activity, use of large doses of DDAVP Nasal Spray with other pressor agents should only be done with careful patient monitoring.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Teratology studies in rats have shown no abnormalities. No further information is available.
Pregnancy-Category B: Reproduction studies performed in rats and rabbits with doses up to 12.5 times the human intranasal dose (i.e. about 125 times the total adult human dose given systemically) have revealed no evidence of harm to the fetus due to desmopressin acetate. There are several publications of management of diabetes insipidus in pregnant women with no harm to the fetus reported; however, no controlled studies in pregnant women have been carried out. Published reports stress that, as opposed to preparations containing the natural hormones, DDAVP Nasal Spray (desmopressin acetate) in antidiuretic doses has no uterotonic action, but the physician will have to weigh possible therapeutic advantages against possible dangers in each individual case.
Nursing Mothers: There have been no controlled studies in nursing mothers. A single study in a post-partum woman demonstrated a marked change in plasma, but little if any change in assayable DDAVP Nasal Spray in breast milk following an intranasal dose of 10 mcg.
Pediatric Use: Primary Nocturnal Enuresis: DDAVP Nasal Spray has been used in childhood nocturnal enuresis. Short-term (4-8 weeks) DDAVP Nasal Spray administration has been shown to be safe and modestly effective in children aged 6 years or older with severe childhood nocturnal enuresis. Adequately controlled studies with DDAVP Nasal Spray in primary nocturnal enuresis have not been conducted beyond 4-8 weeks. The dose should be individually adjusted to achieve the best results.
Central Cranial Diabetes Insipidus: DDAVP Nasal Spray has been used in children with diabetes insipidus. Use in infants and children will require careful fluid intake restriction to prevent possible hyponatremia and water intoxication. The dose must be individually adjusted to the patient with attention in the very young to the danger of an extreme decrease in plasma osmolality with resulting convulsions. Dose should start at 0.05 mL or less.
Since the spray cannot deliver less than 0.1 mL (10 mcg), smaller doses should be administered using the rhinal tube delivery system. Do not use the nasal spray in pediatric patients requiring less than 0.1 mL (10 mcg) per dose.
There are reports of an occasional change in response with time, usually greater than 6 months. Some patients may show a decreased responsiveness, others a shortened duration of effect. There is no evidence this effect is due to the development of binding antibodies but may be due to a local inactivation of the peptide.
ADVERSE REACTIONS: Infrequently, high dosages have produced transient headache and nausea. Nasal congestion, rhinitis and flushing have also been reported occasionally along with mild abdominal cramps. These symptoms disappeared with reduction in dosage. Nose-bleed, sore throat, cough and upper respiratory infections have also been reported.
The following table lists the percent of patients having adverse experiences without regard to relationship to study drug from the pooled pivotal study data for nocturnal enuresis.

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

OVERDOSAGE: See adverse reactions above. In case of overdosage, the dose should be reduced, frequency of administration decreased, or the drug withdrawn according to the severity of the condition. There is no known specific antidote for DDAVP Nasal Spray. An oral LD_{50} has not been established. An intravenous dose of 2 mg/kg in mice demonstrated no effect.
HOW SUPPLIED: A 5-mL bottle with spray pump delivering 50 doses of 10 mcg (NDC 0075-2450-02). Also available as 2.5 mL per vial, packaged with two rhinal tube applicators per carton (NDC 0075-2450-01). Keep refrigerated at 2°-8°C (36°-46°F). When traveling, product will maintain stability for up to 3 weeks when stored at room temperature, 22°C (72°F).
CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.
Please see full prescribing information in product circular.

References: 1. Roth D: Introduction to *Current Concepts in the Management of Primary Nocturnal Enuresis*. Proceedings from a symposium sponsored by the Baylor College of Medicine: January 1991. 2. Miller K, Goldberg S, Atkin B: Nocturnal enuresis: Experience with long-term use of intranasally administered desmopressin. *J Pediatr* 1989;114(Part 2):723-726. 3. Harris AS: Clinical experience with desmopressin: Efficacy and safety in central diabetes insipidus and other conditions. *J Pediatr* 1989;114(Part 2):711-718. 4. Rittig S, Knudsen UB, Sorenson S, et al: Long-term double-blind cross-over study of desmopressin intranasal spray in the management of nocturnal enuresis. In: Meadow SR, ed. *Desmopressin in Nocturnal Enuresis: Proceedings of an International Symposium*. England: Horus Medical Publications; 1988:43-55. 5. Aladjem M, Wohl R, Boichis H, et al: Desmopressin in nocturnal enuresis. *Arch Dis Child* 1982;57:137-140. 6. Baker BL: Symptom treatment and symptom substitution in enuresis. *J Abnorm Psych* 1969;74:42-49. 7. Moffat MEK: Nocturnal enuresis: Psychologic implications of treatment and nontreatment. *J Pediatr* 1989;114(Part 2):697-704.

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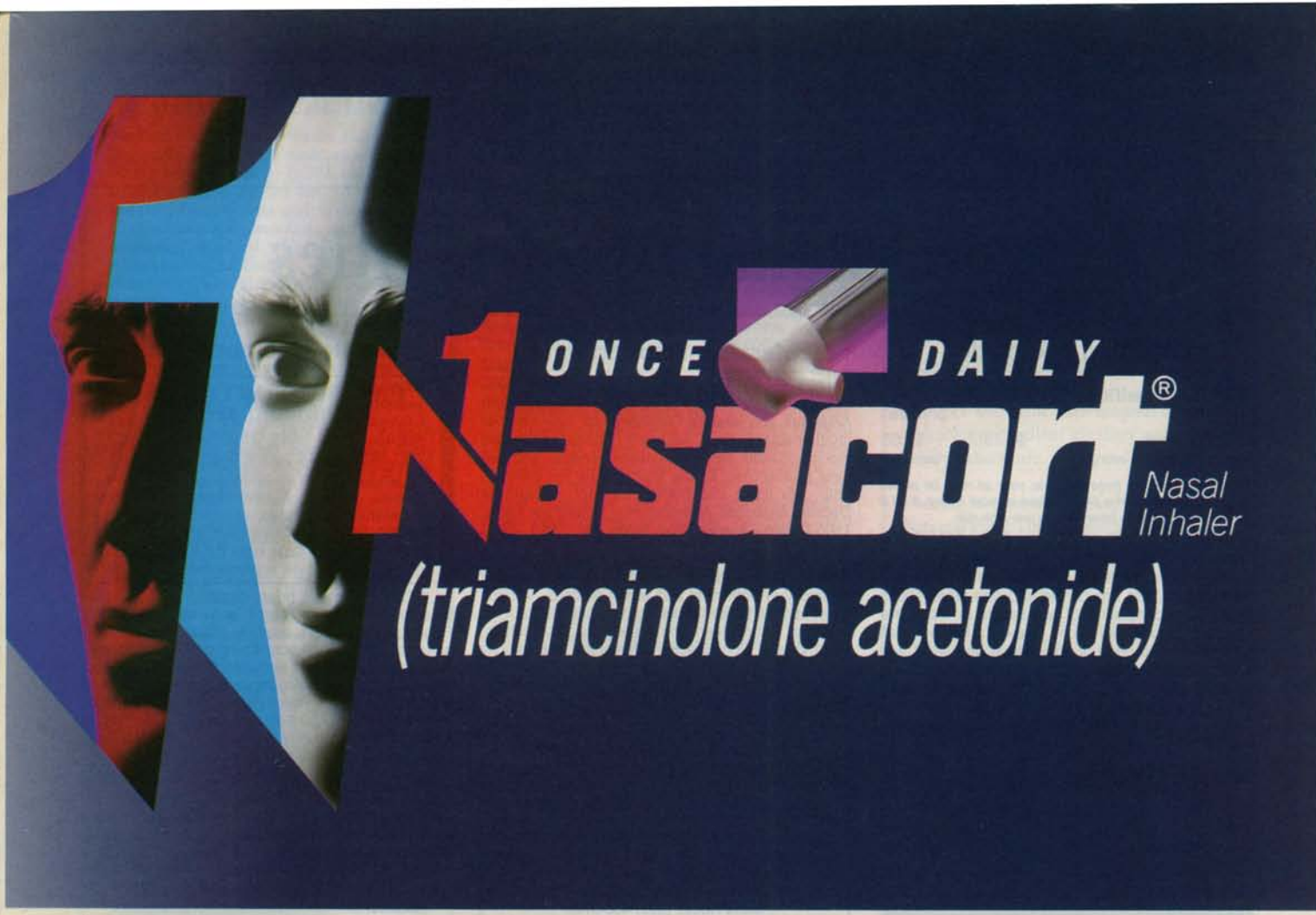

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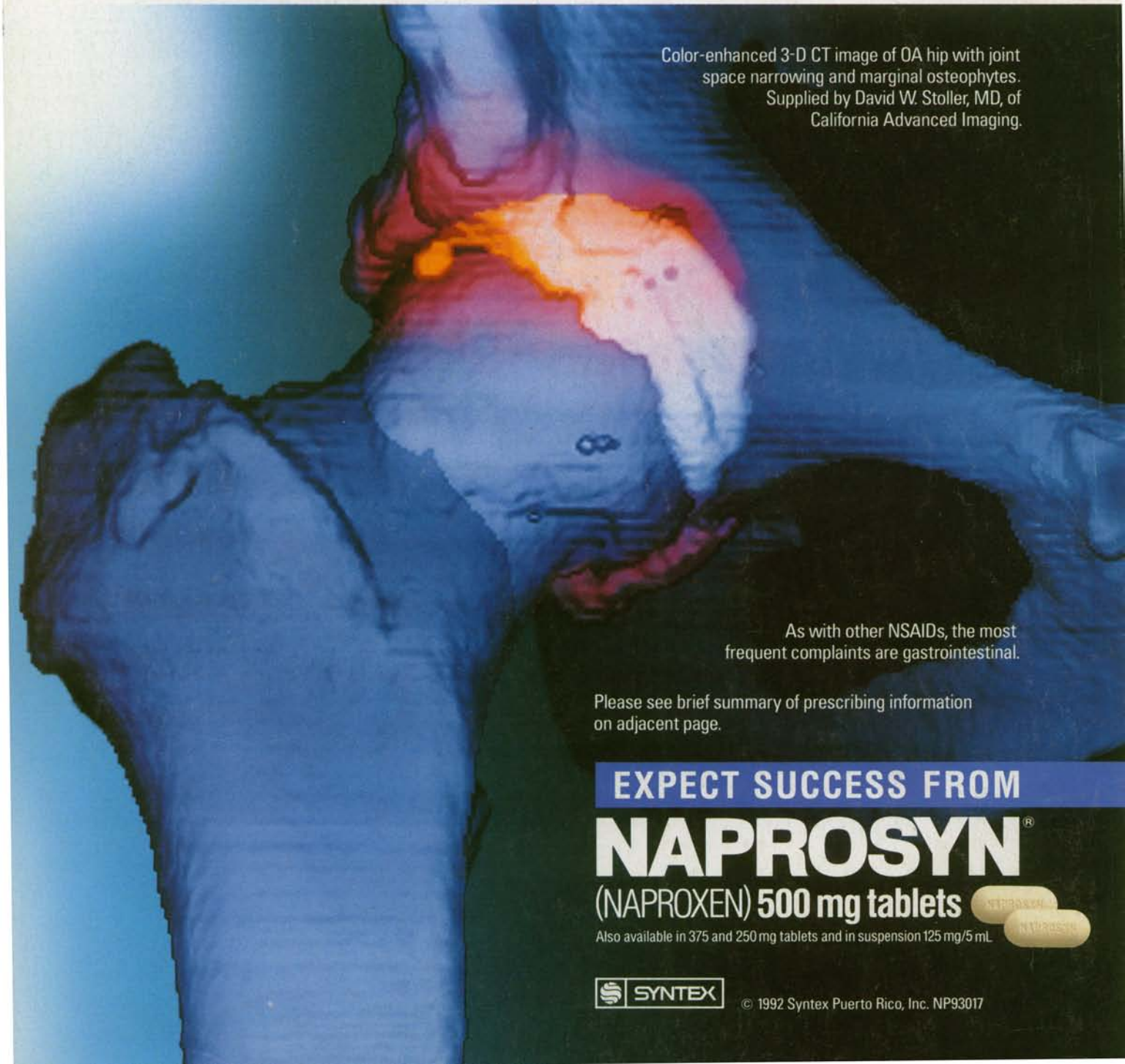
FOR CHRONIC ARTHRITIS

EXPECT A REDUCTION IN JOINT PAIN AND TENDERNESS



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

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

Please see brief summary of prescribing information on adjacent page.

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