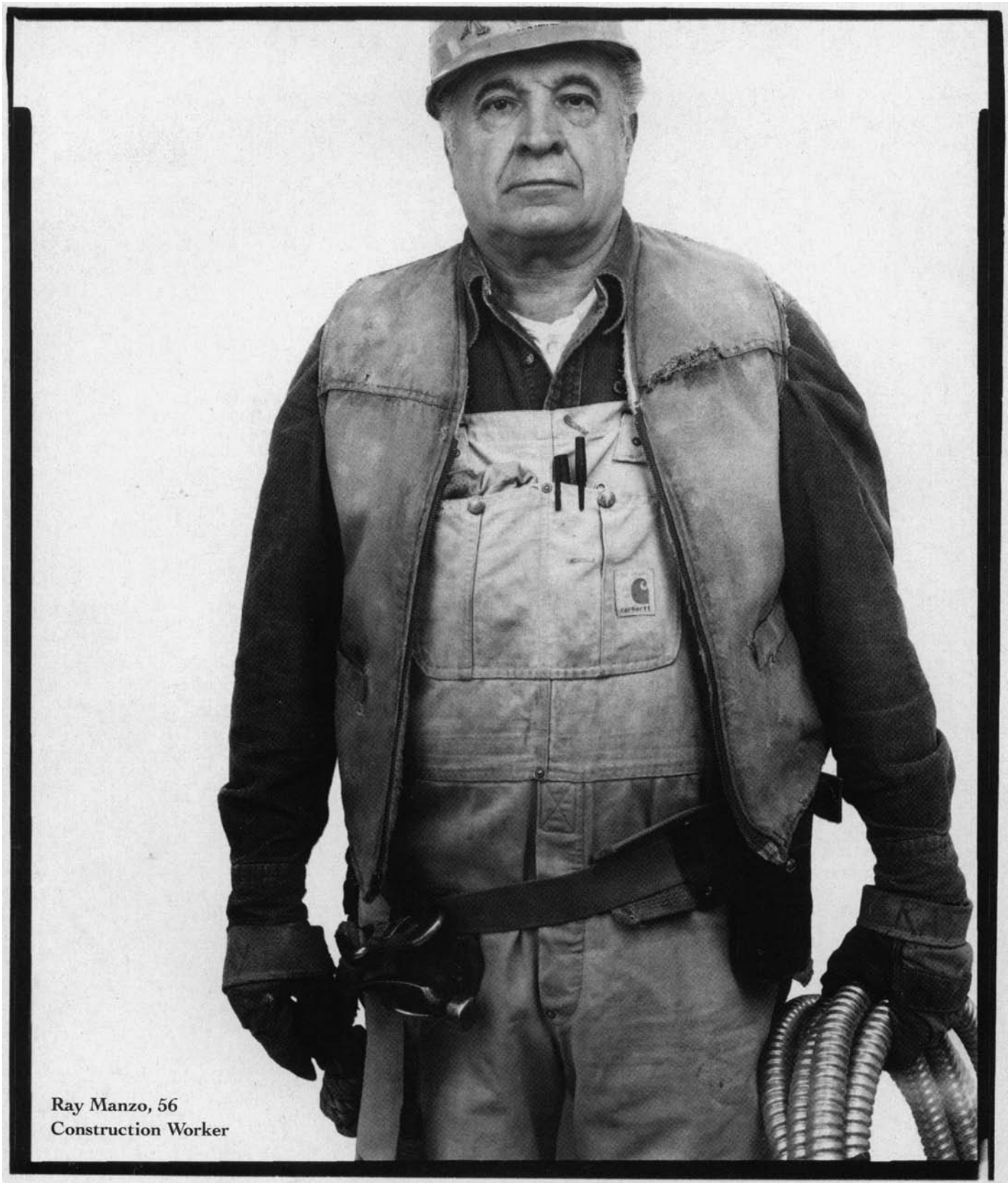


Ray Manzo, 56
Construction Worker

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]

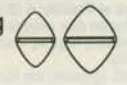
TOUGH PHYSICAL WORK.

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

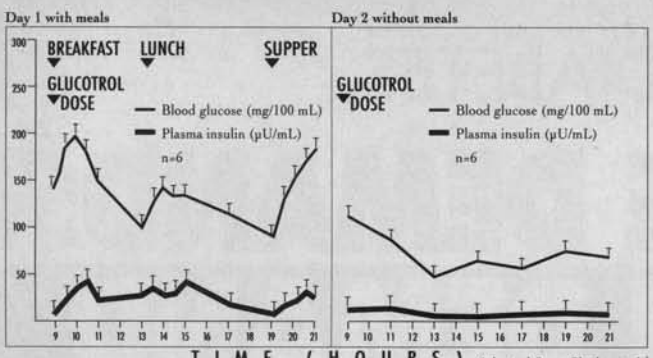


As with all sulfonylureas, hypoglycemia may occur.

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

VERELAN

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

Incidence of side effects commonly associated with calcium channel blockers

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

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

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

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

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

ONCE-A-DAY

VERELAN®

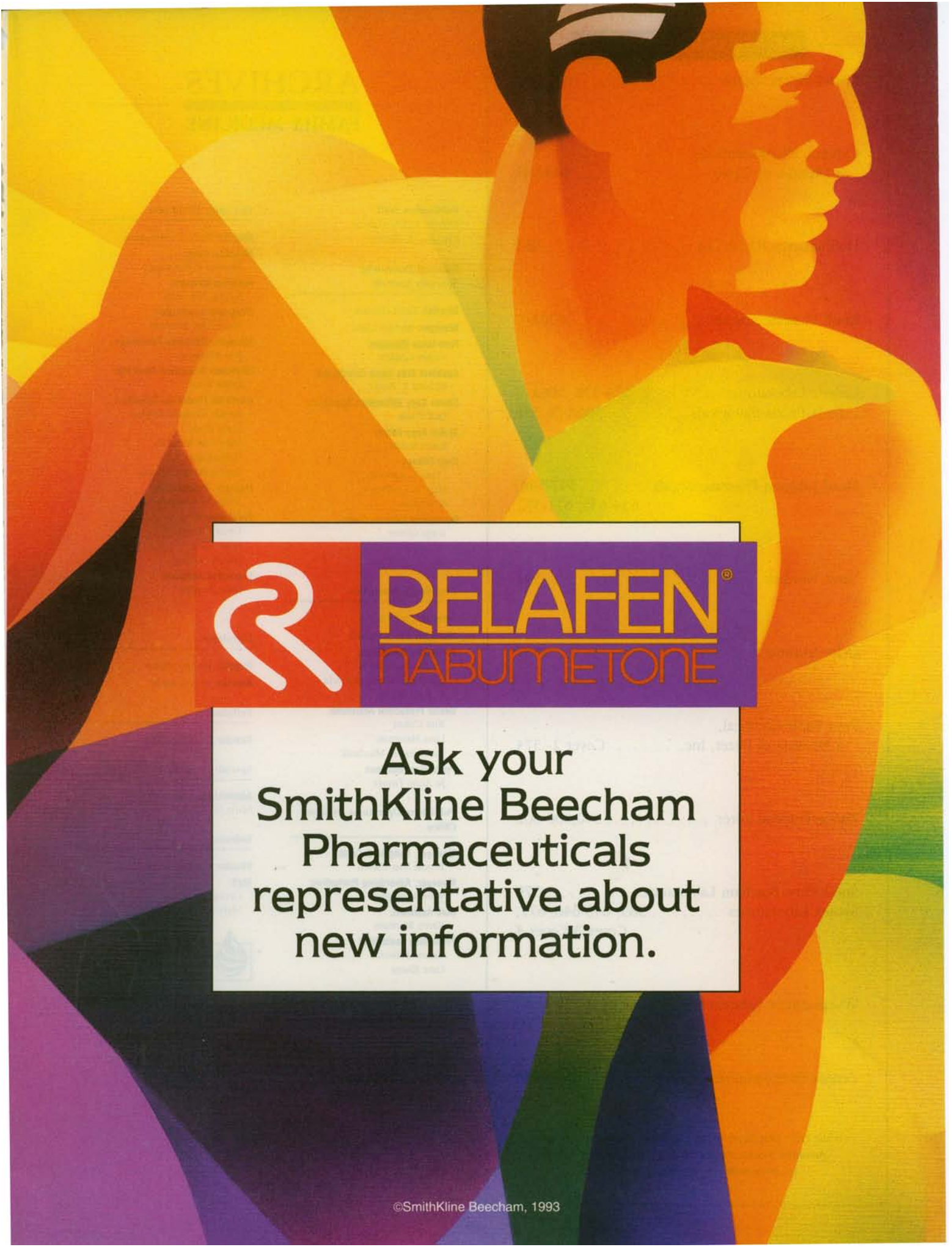
Verapamil HCl 120 mg 180 mg 240 mg

PELLET-FILLED CAPSULES

ARCHIVES OF FAMILY MEDICINE

VOL 2 NO. 6, JUNE 1993

American Medical Association
Physicians dedicated to the health of America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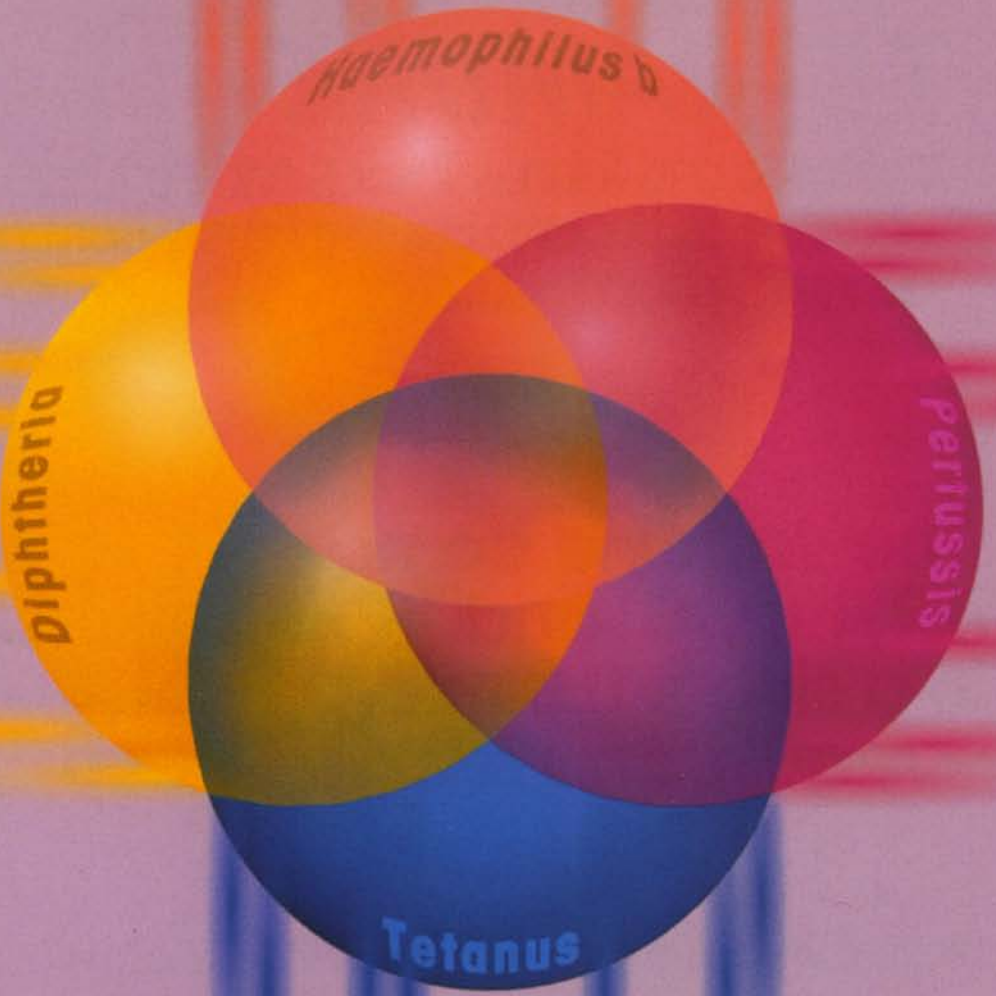

With one exciting new combination vaccine

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.

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- Increase basic science and clinical knowledge in family practice
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- Provide family practicioners with a comprehensive review and update

METHODS

- HOME STUDY MATERIALS with a syllabus of questions and answers – and assignments
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Please see brief summary of prescribing information below.

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

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

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

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

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

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

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

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

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

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

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I recall very early in childhood hearing my family discuss the state of Georgia's proposal for erecting a statue to honor Dr Long in the US Capitol Statuary Hall. My next impression occurred when I was able to visit and see Dr Long's statue in the Statuary Hall in Washington, DC. In 1937, I entered the University of Georgia in Athens, a few miles from Jefferson where Dr Long's office was located, and I had the opportunity to visit his office and see some of his equipment. His office is now a historical landmark, and there are some 30 books, many papers, letters, and other materials available in the Athens libraries on this subject.

The continued esteem in which the people of Georgia hold Dr Long is again being expressed in the designation of his hospital namesake, The Crawford W. Long Hospital (a unit of Emory University), as the official hospital for the 1996 Olympics. This honors Dr Long as the first person to use ether anesthesia for the alleviation of pain during surgical procedures. This remains my bias.

Today, as a physician and medical researcher, I reluctantly admit that I could not find any announcement of Dr Long's discovery or any published results in a recognized medical journal until some years after his discovery. The real truth may never be known.

In spite of the controversy, Dr Long's legacy continues to inspire the people of Georgia, and many others, as a great human being and one of the major early players in the alleviation of surgical pain.

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

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

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

3/20/91 4000-2

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

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

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

63533

Ayerst Laboratories Inc.
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Philadelphia, PA 19101

A·H·ROBINS

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.

Specify "Dispense As Written"

In Mild Hypertension[1]

Dependable Control Is Shaped Like This

Effective in mild hypertension[1*†]

Excellent safety profile[1]

Potassium and magnesium conservation[1,2]

Prescribe the Shape to Remember

Once-a-day **MAXZIDE®-25 MG**

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

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

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

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

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

Specify

"Dispense As Written"

Prescribe the Shape to Remember

Once-a-day **MAXZIDE®-25 MG**

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

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

Brief Summary

Please see package insert for full prescribing information.

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

WARNINGS

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

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

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

PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

MAXZIDE may interfere with quinidine measurement.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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References

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

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

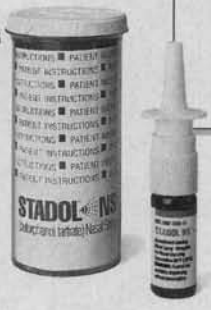
Advantus™ Pharmaceuticals

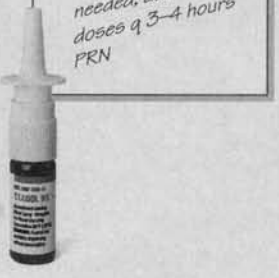
February 1993

8511-2IR

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.

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Princeton, New Jersey 08543
U.S.A.

A4-K004-4-93

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.

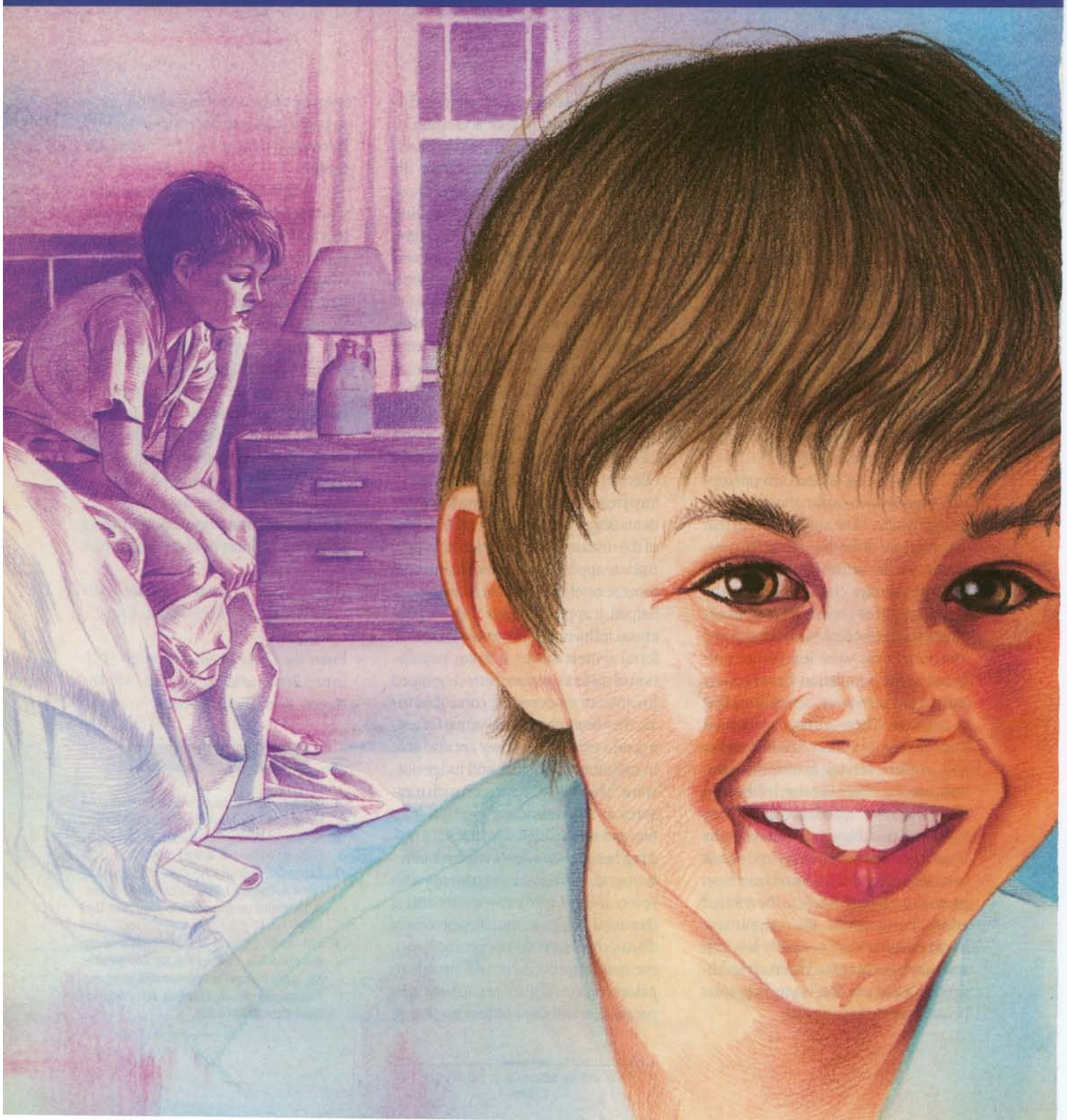
Please see brief summary of prescribing information on following page.

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

Dedicated to Excellence in Women's Health Care

NOW FOR BED-WETTING...

Waking up dry,



morning after morning

DDAVP® Nasal Spray...works hand in hand with behavior modification to help control bed-wetting, a disorder that affects 5 to 7 million children nationwide.[1]

Works safely

- 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.

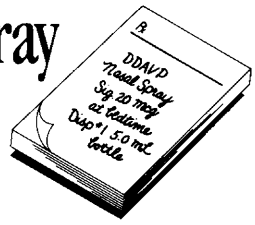
DDAVP® Nasal Spray
(desmopressin acetate) 5mL

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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500 ARCOLA ROAD
COLLEGEVILLE, PA 19426
By Ferring Pharmaceuticals, Malmö, Sweden

FOREST LABORATORIES, INC.

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THE PRAVACHOL® DIRECTION

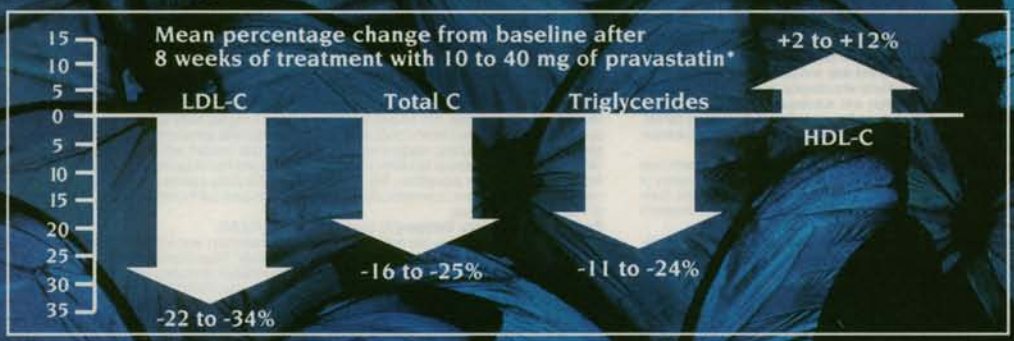
Effective lipid management doesn't have to be tough

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

IN LIPID MANAGEMENT

Effective lipid management—improves key lipids

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



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

Excellent safety/tolerability profile for patients

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

Easy dosing regimen and other patient benefits

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

PRAVACHOL®

pravastatin sodium 20 mg tablets

Bristol-Myers Squibb Company

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

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

PRAVACHOL® (Pravastatin Sodium Tablets)

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

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

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

WARNINGS

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

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

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

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

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

PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

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

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

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

ADVERSE REACTIONS

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

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

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

*Statistically significantly different from placebo.

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

Skeletal: myopathy, rhabdomyolysis.

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

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

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

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

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

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

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

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

OVERDOSAGE

There have been no reports of overdoses with pravastatin.

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

Ask Phyllis her opinion of the anti-stroke drug that lets her hold onto her independence and life savings.

When medicines you prescribe can help patients like Phyllis avoid a stroke, that's obviously a good thing. What's not so apparent is how dramatically the same drugs reduce nursing home costs.

Stroke often leaves survivors so disabled they require nursing home care which now averages over $30,000 a year per patient.

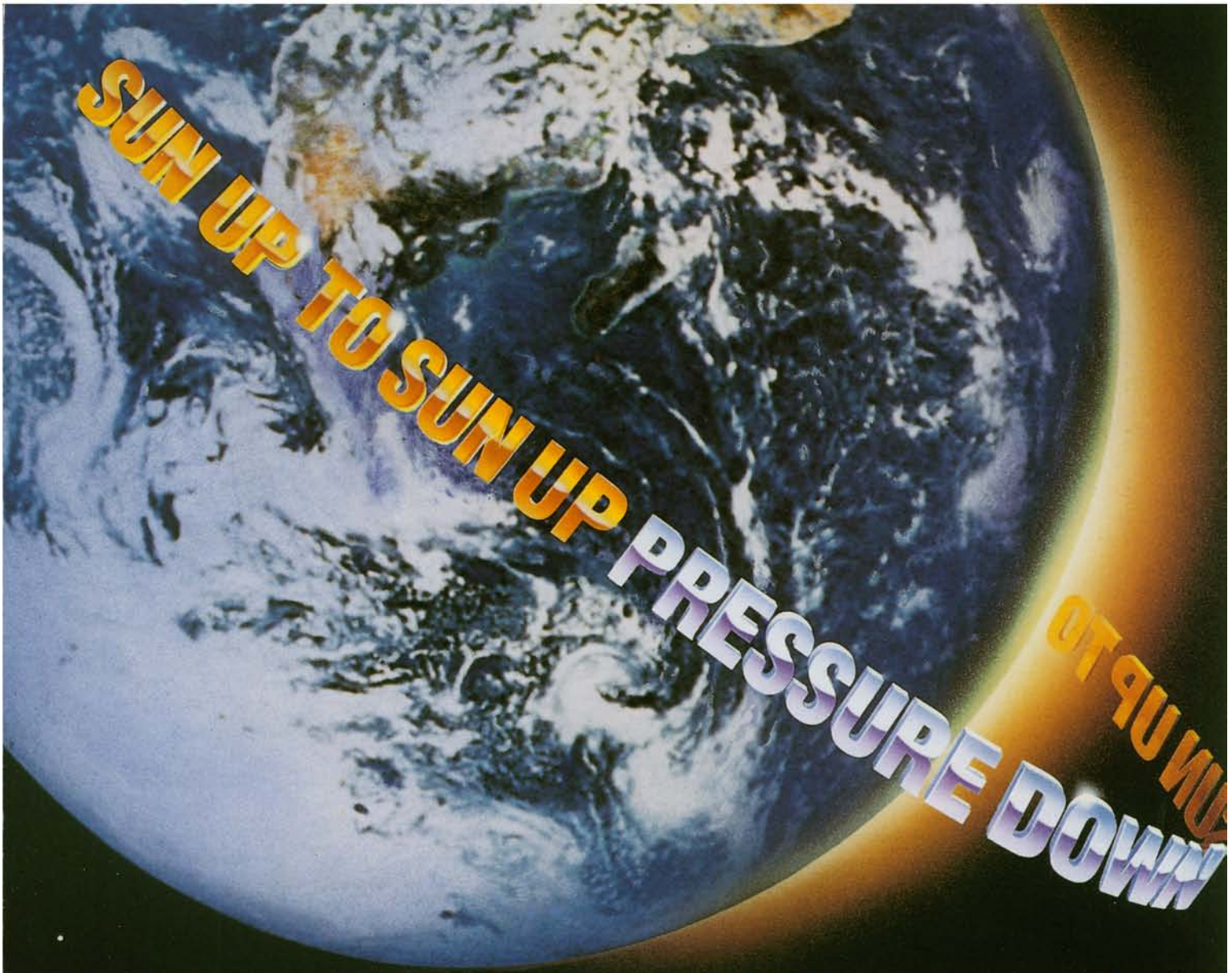
But drugs that reduce the risk of strokes are helping individuals and families avoid such a huge financial blow. And helping to reduce the nation's expenditures for nursing home care, estimated at $66 billion a year.

Prescription drugs can help patients like Phyllis avoid disabling strokes and nursing home care, which averages over $30,000 per year.

America's healthcare crisis calls for this kind of cost-saving power. And new prescription drugs are our best hope for providing it.

For more information on how new medicines improve lives and save money, write or call The Pharmaceutical Manufacturers Association, 1100 Fifteenth Street, N.W., Box PHY, Washington, D.C. 20005. 1-800-538-2692.

PHARMACEUTICALS
Saving Lives. Saving Money.



True once-daily antihypertensive control*

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

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

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

ONCE-DAILY

ISOPTIN SR

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

knoll®

BASF Group

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

Please see back for brief summary of prescribing information.

ONCE-DAILY

ISOPTIN® SR

(verapamil HCl) Sustained-Release Tablets

Unsurpassed dosage flexibility

180 mg

The recommended starting/maintenance dose

240 mg

For patients who require a step up in dosage

120 mg

For elderly or small-stature patients who require lower doses

From the originators of verapamil

knoll

BASF Group

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

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Brief Summary of Prescribing Information

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

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

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

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

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

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

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

DOSAGE AND ADMINISTRATION

Essential Hypertension

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

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

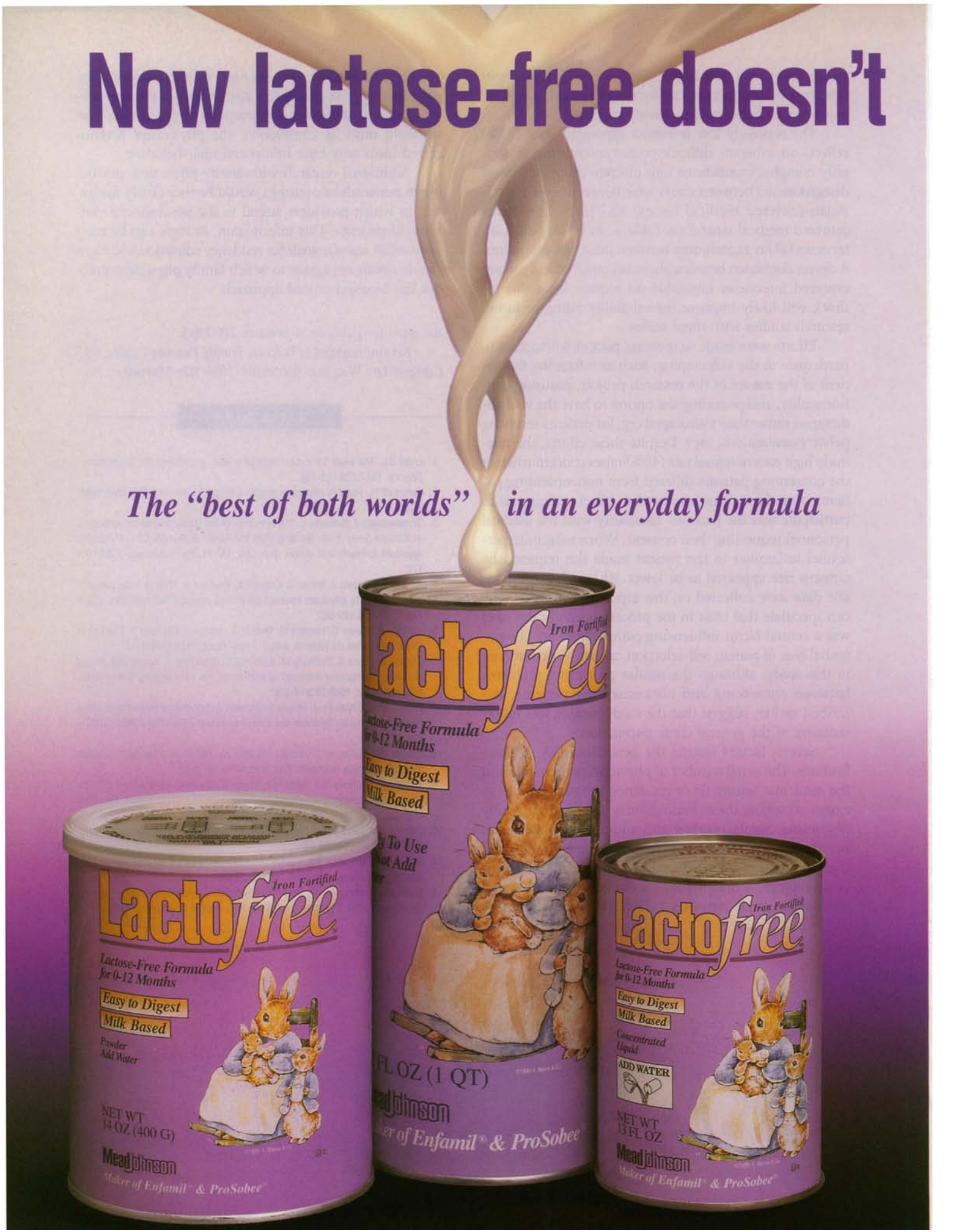
a. 240 mg each morning.
b. 180 mg each morning plus 180 mg each evening, or 240 mg each morning plus 120 mg each evening.
c. 240 mg every twelve hours.

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

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

Now lactose-free doesn't

The "best of both worlds" in an everyday formula



have to mean milk-free!

More like breast milk than other lactose-free formulas

	CARBOHYDRATE	PROTEIN	FAT
Breast Milk	LACTOSE	HUMAN MILK PROTEIN	HUMAN MILK FAT
Milk-Based Formula	LACTOSE	MILK PROTEIN	VEGETABLE OIL BLEND*
Lacto*free*™	**LACTOSE FREE**	**MILK PROTEIN**	**VEGETABLE OIL BLEND**
Soy-Based Formula	LACTOSE FREE	SOY PROTEIN	VEGETABLE OIL BLEND*

The benefits of milk protein without the problems of lactose

- Keeps milk protein–the preferred† protein source–in the infant's diet
- Avoids or resolves common feeding problems associated with lactose:
  – fussiness/crying – gas – diarrhea
- Easy to digest
- No other formula has a fat blend closer to breast milk‡

Recommend...

Lacto*free* *Iron Fortified*

Lactose-Free Formula for Baby's First Year and Beyond

The first milk-based formula§ with the lactose-free difference

* SMA® and Nursoy® (registered trademarks of Wyeth-Ayerst Laboratories, Philadelphia, PA) contain some animal fats.

† Data on file, Mead Johnson & Company

Mead Johnson NUTRITIONALS

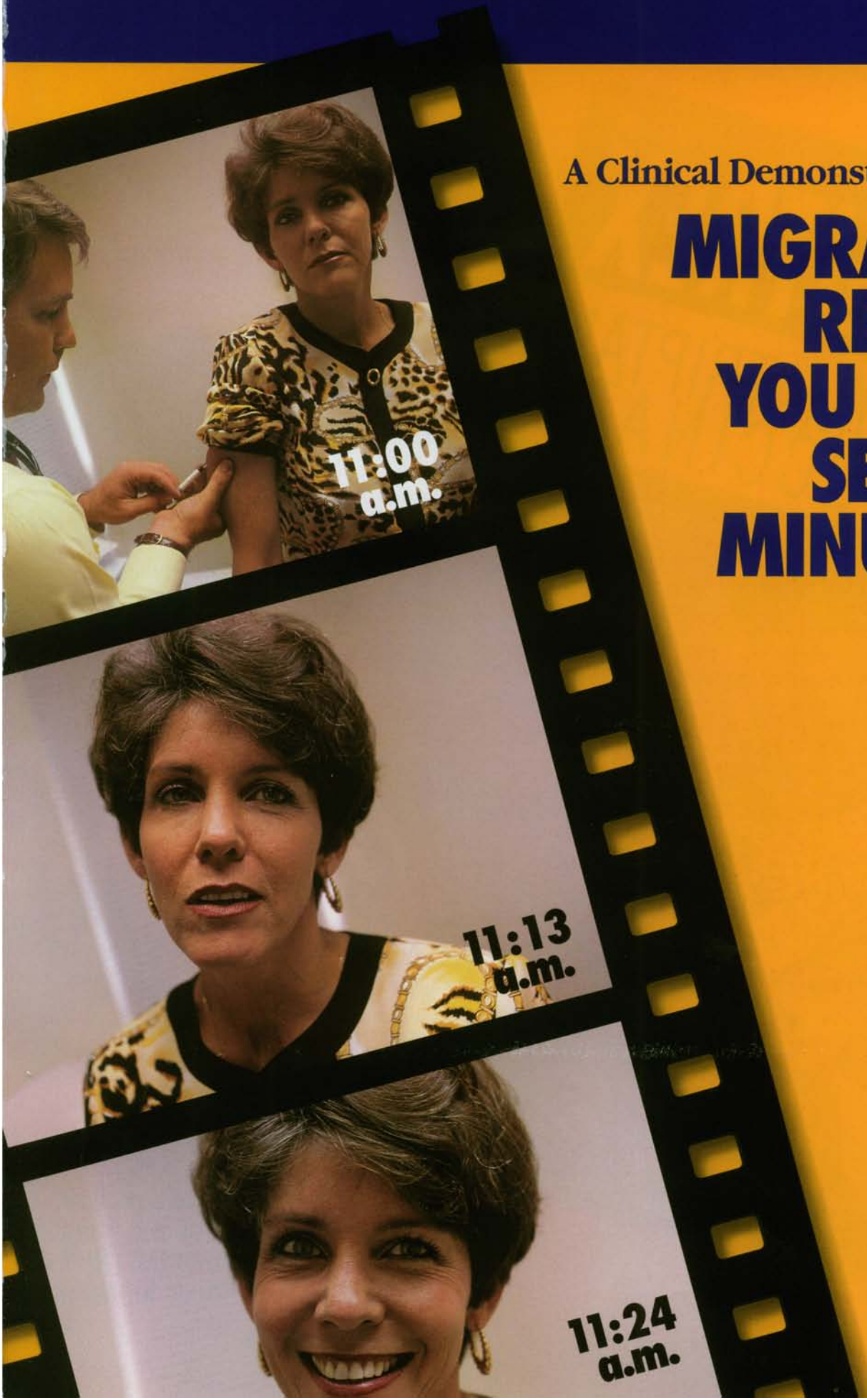
L-K370-4-93

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

§ Based on milk protein isolate

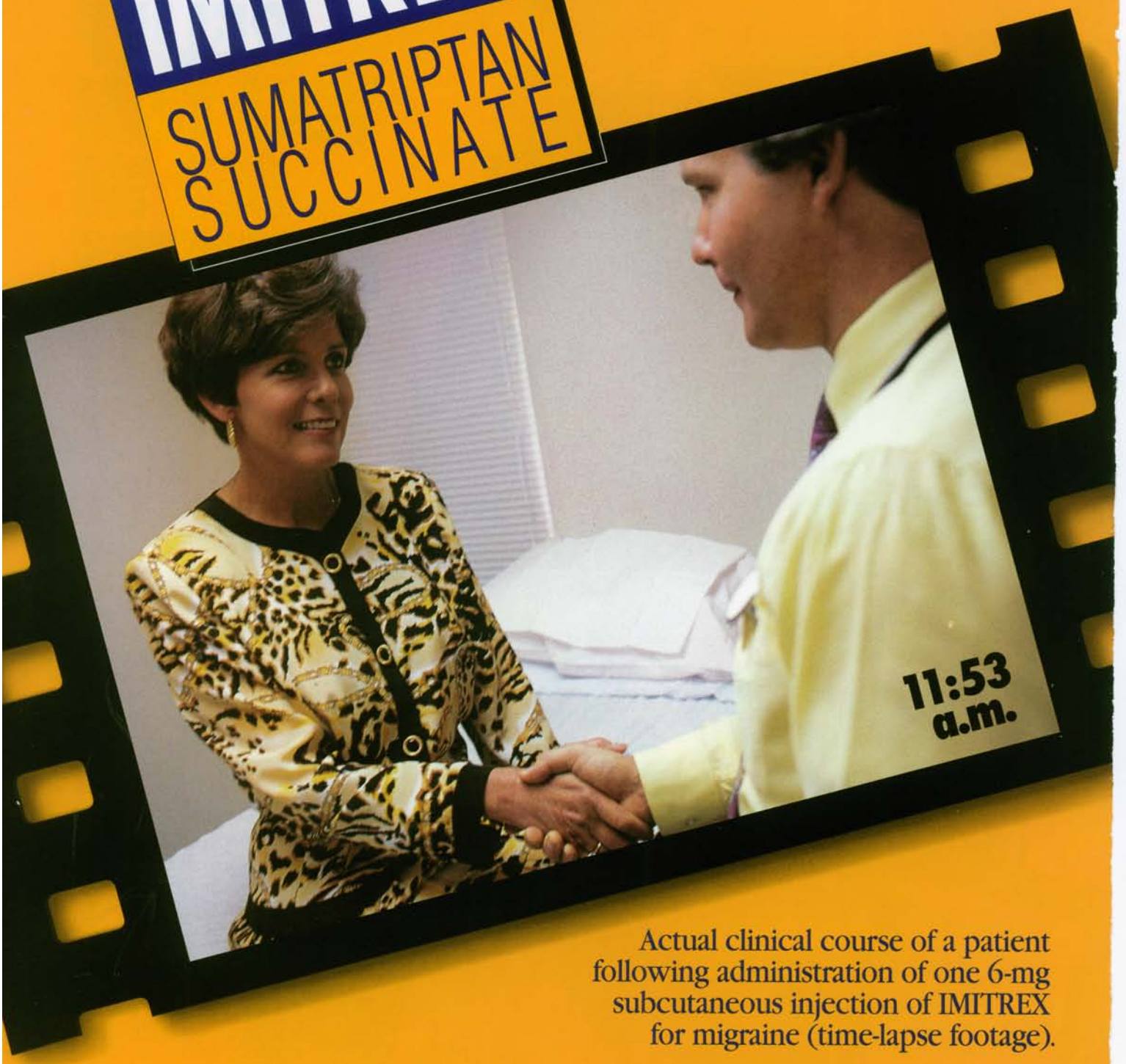
A Clinical Demonstration of

MIGRAINE RELIEF YOU CAN SEE IN MINUTES



CERENEX PHARMACEUTICALS INTRODUCES

NEW SUBCUTANEOUS IMITREX™ SUMATRIPTAN SUCCINATE



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

MIGRAINE RELIEF THAT CAN CHANGE PATIENTS' LIVES

IMITREX is the first highly specific 5-HT$_1$ receptor agonist—offering a profile of relief unlike any other migraine therapy.

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

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

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

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

Relief without sedation.

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

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

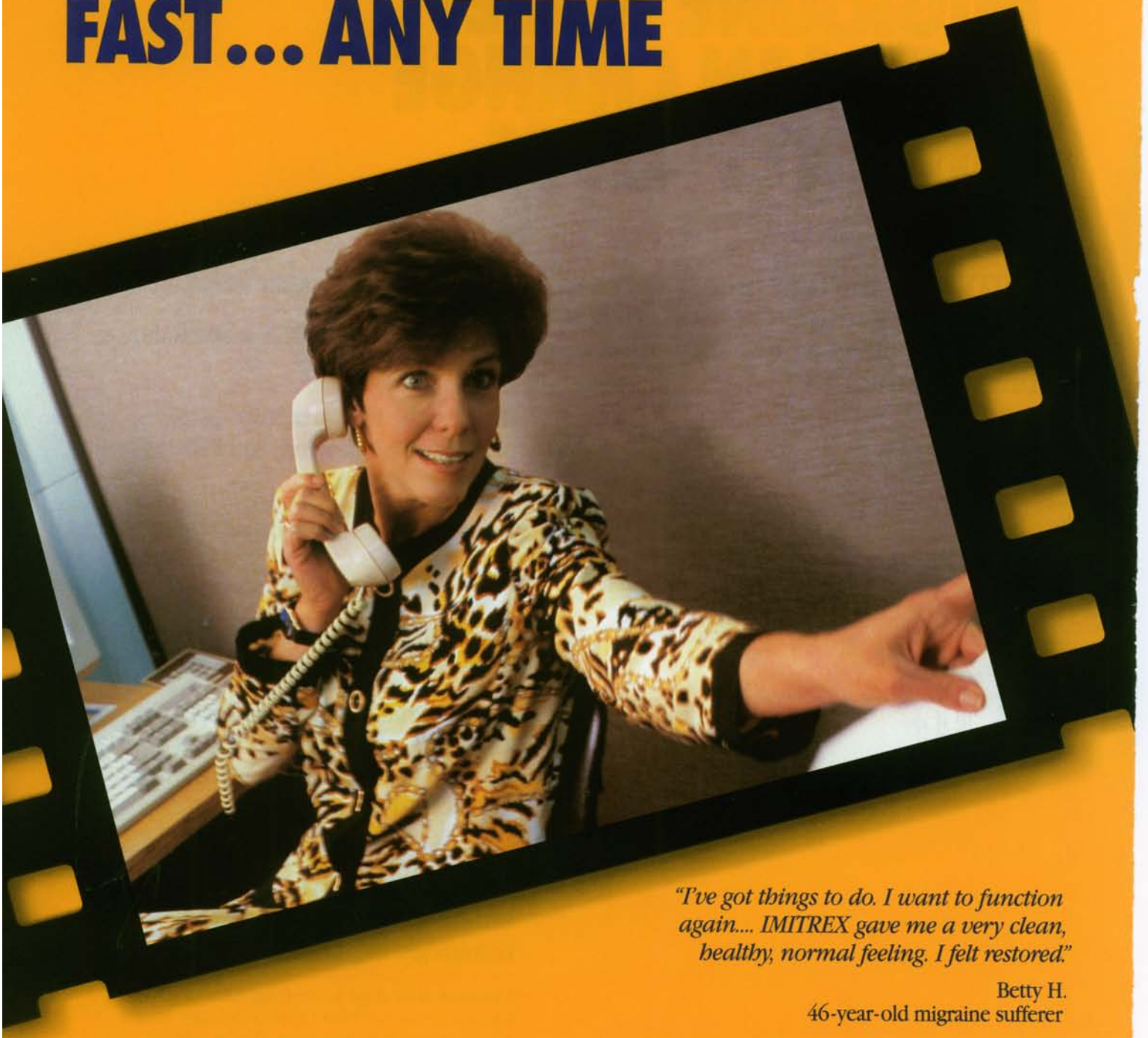
Relief of migraine attacks with or without aura. (IMITREX should not be administered to patients with basilar or hemiplegic migraine.)

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

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

CERENEX PHARMACEUTICALS

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



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

Betty H.
46-year-old migraine sufferer

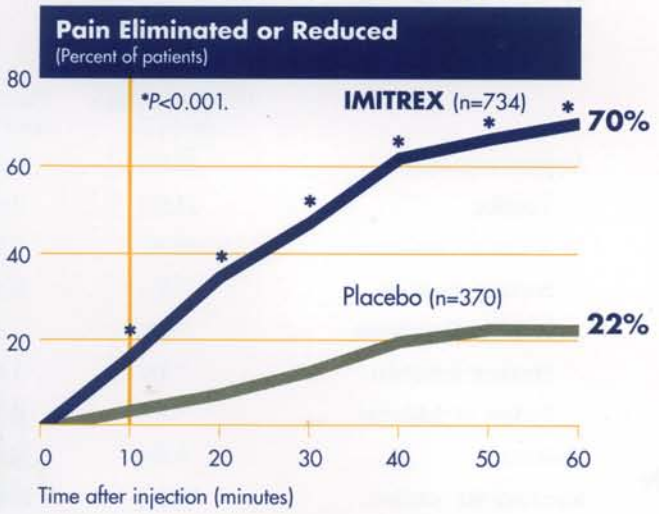
INTRODUCES

NEW SUBCUTANEOUS IMITREX™ SUMATRIPTAN SUCCINATE

MIGRAINE RELIEF THAT CAN CHANGE PATIENTS' LIVES

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

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



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

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

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

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

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

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

RELIEF WITHOUT COMPROMISE

IMITREX is highly selective.

IMITREX is nonsedating.

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

Cardiovascular considerations

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

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

Pregnancy category C

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

Worldwide clinical experience

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

Reported adverse events are generally mild and transient.

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

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

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

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

INTRODUCES

NEW SUBCUTANEOUS IMITREX™ SUMATRIPTAN SUCCINATE

MIGRAINE RELIEF THAT CAN CHANGE PATIENTS' LIVES

RELIEF WITHIN REACH FOR PATIENTS

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

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

High patient acceptance.[4]

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

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

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

IMITREX offers simple, convenient dosing.

The recommended dose is one 6-mg subcutaneous injection.

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

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

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

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

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

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

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

BRIEF SUMMARY

Imitrex™ (sumatriptan succinate) Injection

For Subcutaneous Use Only.

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

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

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

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

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

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

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

Imitrex Injection is contraindicated in patients with hypersensitivity to sumatriptan.

WARNINGS:

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

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

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

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

Use in Women of Childbearing Potential: (see PRECAUTIONS)

PRECAUTIONS:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Eye: Infrequent was irritation of the eye.

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

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

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

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

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

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

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

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

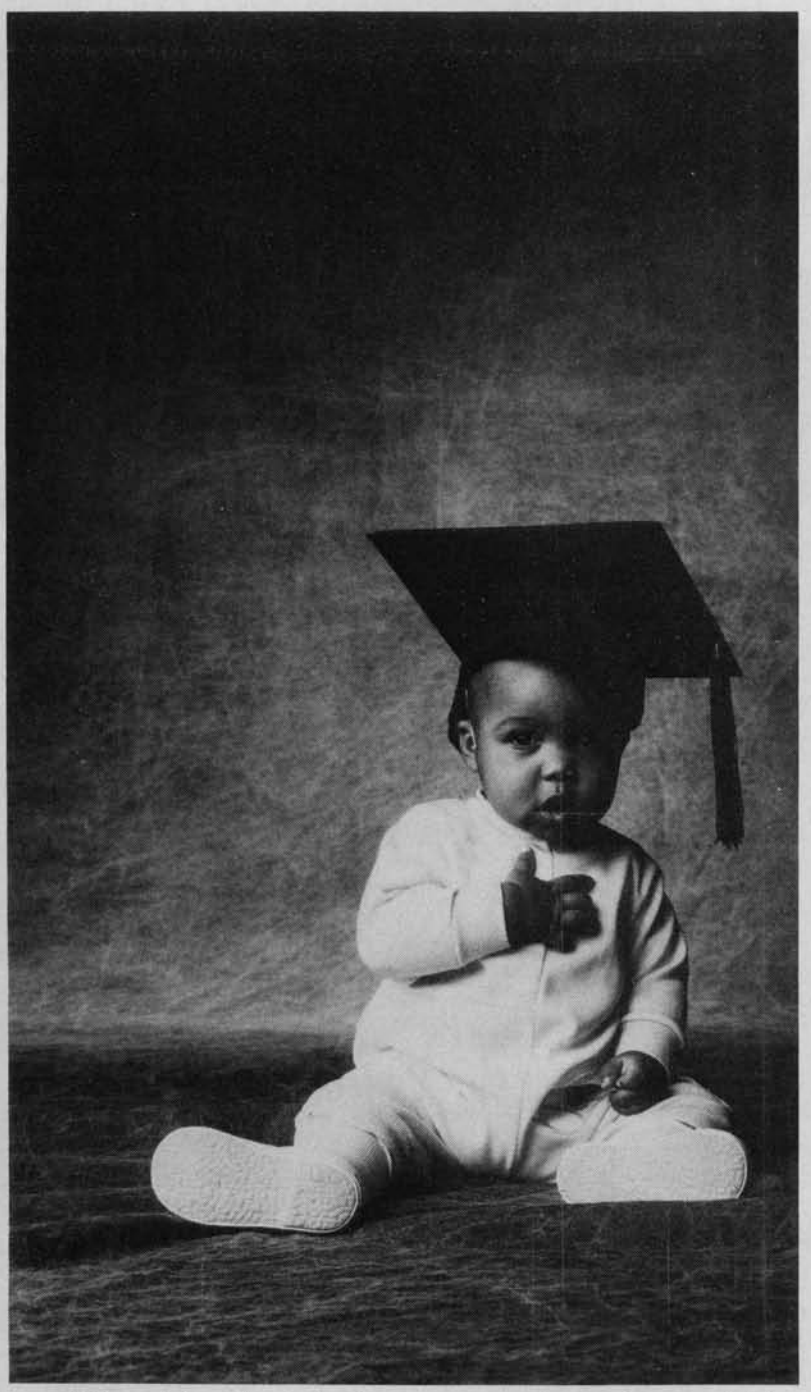
DRUG ABUSE AND DEPENDENCE: The abuse potential of Imitrex™ Injection cannot be fully delineated in advance of extensive marketing experience. One clinical study enrolling 12 patients with a history of substance abuse failed to induce subjective behavior and/or physiologic response ordinarily associated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

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

January 1993 SUC5

IMX063 Printed in USA April 1993

U.S. Savings Bonds Are Now Tax Free For College. Good News Today. Better News In 18 Years.



If the cost of a college education seems expensive now, imagine what it will be in 18 years. That's why when it comes to college, Bonds are better than ever before. For years, they've been exempt from state and local income tax. Now, Bonds bought for your children's education can also be free from federal income tax. Which means most people can keep every penny of the interest they earn.

Start your tax free tuition fund today. Buy Bonds at your local bank, or ask about the Payroll Savings Plan at work.

U.S. Savings Bonds

The Great American Investment

A public service of this publication.

NAPROSYN®

(NAPROXEN) 500 mg tablets

Brief Summary:

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

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

SYNTEX

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

Rev. 39 September 1990

IN MANY CHRONIC ARTHRITIS PATIENTS

Expect Success from the #1 Prescribed NSAID*

Color-enhanced 3-D MRI of OA knee with medial compartment narrowing and anterior osteophytes in red. Supplied by David W. Stoller, MD, of California Advanced Imaging.

Color-enhanced barium contrast study of stomach.

A proven efficacy and safety profile backed by 16 years of clinical success.

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

Please see brief summary of prescribing information on adjacent page.

EXPECT SUCCESS FROM NAPROSYN®

(NAPROXEN) **500 mg tablets**

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

*Leading industry audits for 12 months ending April 1992. Pharmacy sales of Naprosyn (naproxen) in the U.S. Data on file, Syntex Laboratories, Inc, Document NP92181-A.

SYNTEX

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 were these reactions were volunteered. Where frequency of adverse effects of TENORMIN and placebo is similar, causal relationship to TENORMIN is uncertain.

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

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

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

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

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

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

Reasons for Reduced Dosage

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

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

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

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

Hematologic: Agranulocytosis.

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

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

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Erythematous rash, Raynaud's phenomenon.

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

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

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

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

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

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

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

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

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

BRONCHOSPASM: A beta, 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.

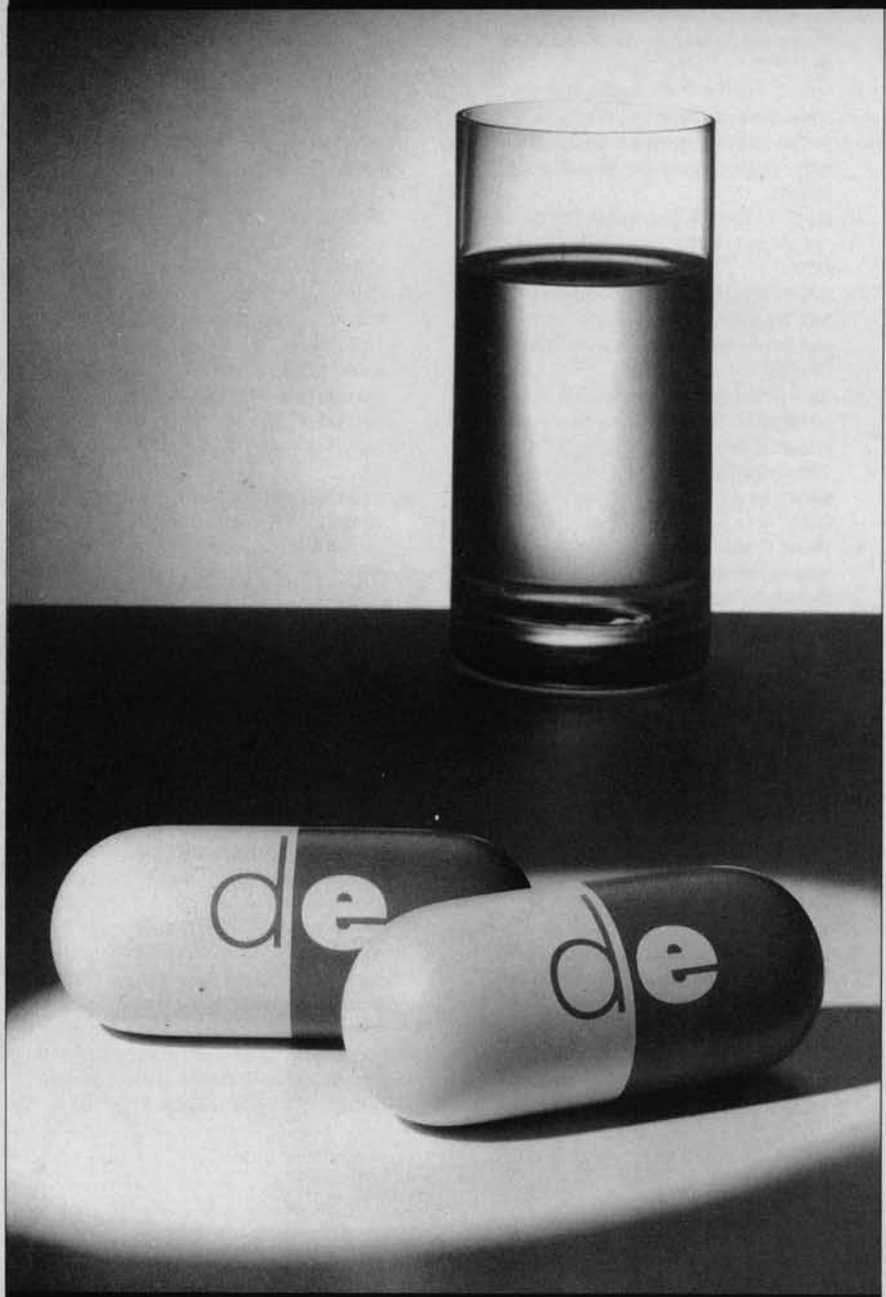
Protect from light. Keep ampules in outer packaging until time of use. Store at room temperature.

REV Y 03/92

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

FSA-1511 ICI-2870R

Strong medicine.



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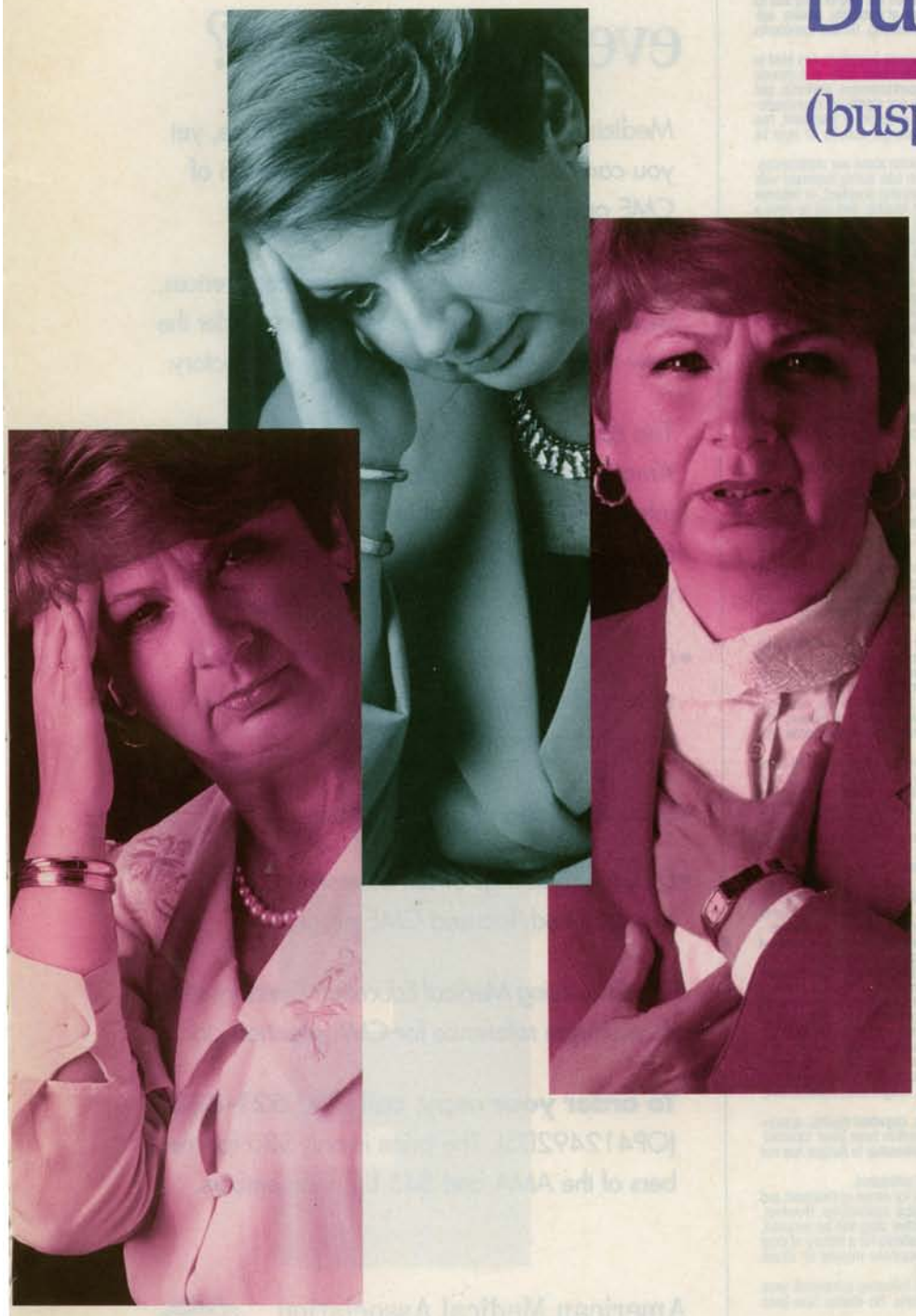
BECAUSE APPROXIMATELY 60% OF PATIENTS WITH PERSISTENT ANXIETY MAY EXHIBIT DEPRESSIVE SYMPTOMS...[1]



BuSpar® 10mg

(buspirone HCl)

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

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

Progressive Relief of Persistent Anxiety.

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

Please see references and brief summary on adjacent page.

BuSpar® (buspirone HCl)

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

Contraindications: Hypersensitivity to buspirone hydrochloride.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

MJL8-4270R2

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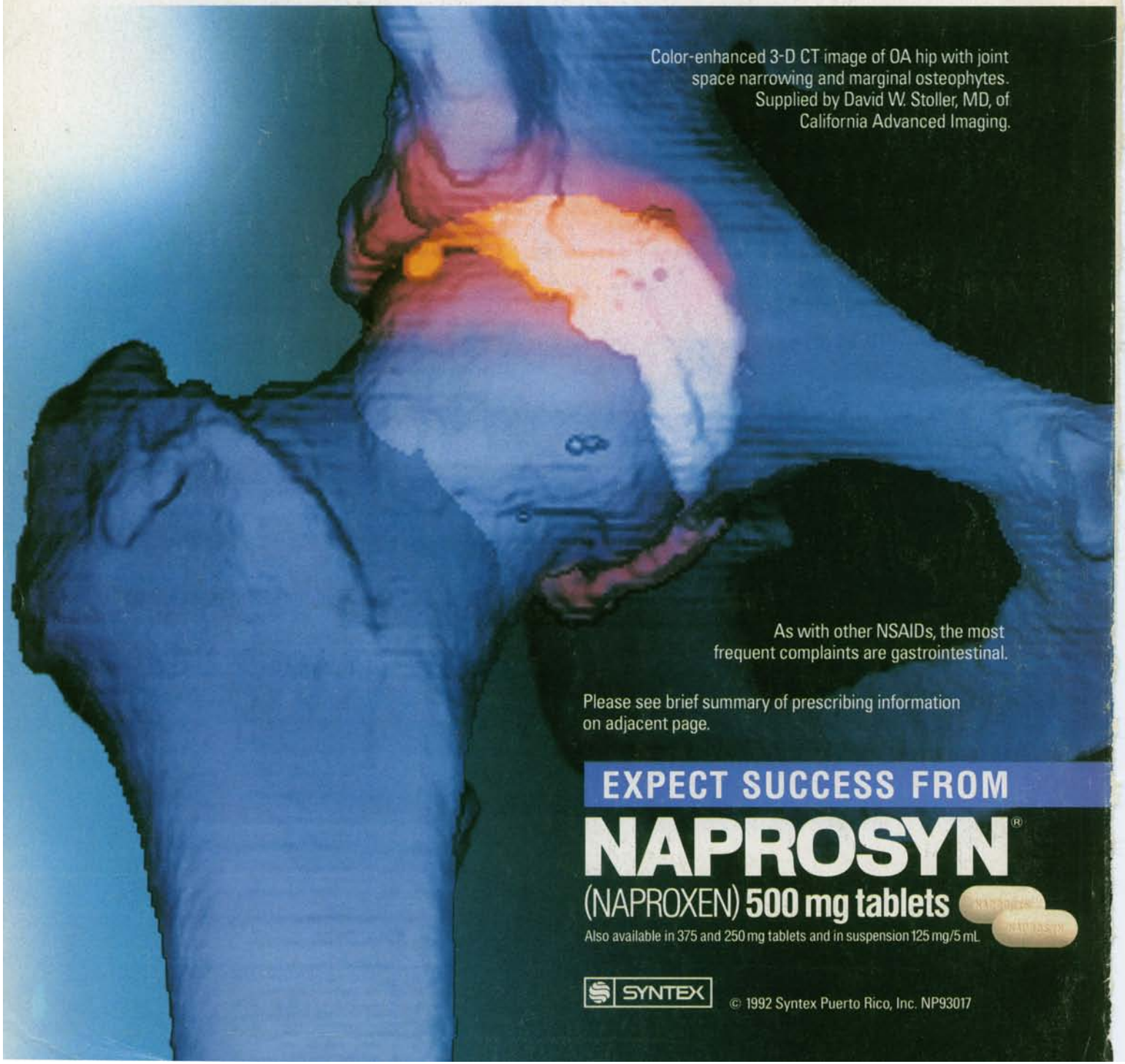

Color-enhanced 3-D CT image of OA hip with joint space narrowing and marginal osteophytes. Supplied by David W. Stoller, MD, of California Advanced Imaging.

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

Please see brief summary of prescribing information on adjacent page.

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