Hypertension may be just the tip of the iceberg.

PLENDIL often represents a prudent choice for patients whose hypertension is accompanied by one or more concomitant disorders.

These may include: hypercholesterolemia, diabetes, impaired renal function, COPD, or asthma.

PLENDIL provides a favorable hemodynamic profile and is generally well tolerated when administered at usual doses. Peripheral edema, generally mild, is the most common adverse event.

PLENDIL provides a gradual onset of action and continuous 24-hour blood-pressure control with convenient once-daily dosing.

PLENDIL. A highly effective calcium channel blocker for hypertension.

For many patients with or without concomitant disorders.*

Plendil®

(felodipine) Tablets, 5 mg, 10 mg

Because you consider the whole patient.

*Safety in patients with heart failure has not been established.

Please see brief summary of Prescribing Information on page following next page.

A/M GROUP
of MERCK & CO., Inc.


FRASER

BRIEF SUMMARY

TABLETS

PLENDIL®

(FELODIPINE)

EXTENDED-RELEASE TABLETS

INDICATIONS AND USAGE

PLENDIL* is indicated for the treatment of hypertension. PLENDIL may be used alone or concomitantly with other antihypertensive agents.

CONTRAINDICATIONS

PLENDIL is contraindicated in patients who are hypersensitive to this product.

PRECAUTIONS

General

Hypotension: Felodipine, like other calcium antagonists, may occasionally precipitate significant hypotension and rarely syncope. It may lead to reflex tachycardia which in susceptible individuals may precipitate angina pectoris. (See ADVERSE REACTIONS.)

Heart Failure: Although acute hemodynamic studies in a small number of patients with NYHA Class II or III heart failure treated with felodipine have not demonstrated negative inotropic effects, safety in patients with heart failure has not been established. Caution therefore should be exercised when using PLENDIL in patients with heart failure or compromised ventricular function, particularly in combination with a beta blocker.

Elderly Patients or Patients with Impaired Liver Function: Patients over 65 years of age or patients with impaired liver function may have elevated plasma concentrations of felodipine and may therefore respond to lower doses of PLENDIL. These patients should have their blood pressure monitored closely during dosage adjustment of PLENDIL and should rarely require doses above 10 mg. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION sections of complete Prescribing Information.)

Peripheral Edema: Peripheral edema, generally mild and not associated with generalized fluid retention, was the most common adverse event in the clinical trials. The incidence of peripheral edema was both dose- and age-dependent. Frequency of peripheral edema ranged from about 10 percent in patients under 50 years of age taking 5 mg daily to about 30 percent in those over 60 years of age taking 20 mg daily. This adverse effect generally occurs within 2-3 weeks of the initiation of treatment.

Information for Patients

Patients should be instructed to take PLENDIL whole and not to crush or chew the tablets. They should be told that mild gingival hyperplasia (gum swelling) has been reported. Good dental hygiene decreases its incidence and severity.

NOTE: As with many other drugs, certain advice to patients being treated with PLENDIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions

Beta-Blocking Agents: A pharmacokinetic study of felodipine in conjunction with metoprolol demonstrated no significant effects on the pharmacokinetics of felodipine. The AUC and C_{max} of metoprolol, however, were increased approximately 31 and 38 percent, respectively. In controlled clinical trials, however, beta blockers including metoprolol were concurrently administered with felodipine and were well tolerated.

Cimetidine: In healthy subjects pharmacokinetic studies showed an approximately 50 percent increase in the area under the plasma concentration time curve (AUC) as well as the C_{max} of felodipine when given concomitantly with cimetidine. It is anticipated that a clinically significant interaction may occur in some hypertensive patients. Therefore, it is recommended that low doses of PLENDIL be used when given concomitantly with cimetidine.

Digoxin: When given concomitantly with felodipine the peak plasma concentration of digoxin was significantly increased. There was, however, no significant change in the AUC of digoxin.

Anticonvulsants: In a pharmacokinetic study, maximum plasma concentrations of felodipine were considerably lower in epileptic patients on long-term anticonvulsant therapy (e.g., phenytoin, carbamazepine, or phenobarbital) than in healthy volunteers. In such patients, the mean area under the felodipine plasma concentration-time curve was also reduced to approximately six percent of that observed in healthy volunteers. Since a clinically significant interaction may be anticipated, alternative antihypertensive therapy should be considered in these patients.

Other Concomitant Therapy: In healthy subjects there were no clinically significant interactions when felodipine was given concomitantly with indomethacin or spironolactone.

Interaction with Food: See CLINICAL PHARMACOLOGY, *Pharmacokinetics and Metabolism* section of complete Prescribing Information.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a two-year carcinogenicity study in rats fed felodipine at doses of 7.7, 23.1 or 69.3 mg/kg/day (up to 28 times' the maximum recommended human dose on a mg/m² basis), a dose related increase in the incidence of benign interstitial cell tumors of the testes (Leydig cell tumors) was observed in treated male rats. These tumors were not observed in a similar study in mice at doses up to 138.6 mg/kg/day (28 times' the maximum recommended human dose on a mg/m² basis). Felodipine, at the doses employed in the two-year rat study, has been shown to lower testicular testosterone and to produce a corresponding increase in serum luteinizing hormone in rats. The Leydig cell tumor development is possibly secondary to these hormonal effects which have not been observed in man.

In this same rat study a dose-related increase in the incidence of focal squamous cell hyperplasia compared to control was observed in the esophageal groove of male and female rats in all dose groups. No other drug-related esophageal or gastric pathology was observed in the rats or with chronic administration in mice and dogs. The latter species, like man, has no anatomical structure comparable to the esophageal groove.

Felodipine was not carcinogenic when fed to mice at doses of up to 138.6 mg/kg/day (28 times' the maximum recommended human dose on a mg/m² basis) for periods of up to 80 weeks in males and 99 weeks in females.

Felodipine did not display any mutagenic activity *in vitro* in the Ames microbial mutagenicity test or in the mouse lymphoma forward mutation assay. No clastogenic potential was seen *in vivo* in the mouse micronucleus test at oral doses up to 2500 mg/kg (506 times' the maximum recommended human dose on a mg/m² basis) or *in vitro* in a human lymphocyte chromosome aberration assay.

A fertility study in which male and female rats were administered doses of 3.8, 9.6 or 26.9 mg/kg/day showed no significant effect of felodipine on reproductive performance.

Pregnancy

Pregnancy Category C

Teratogenic Effects: Studies in pregnant rabbits administered doses of 0.46, 1.2, 2.3 and 4.6 mg/kg/day (from 0.4 to 4 times' the maximum recommended human dose on a mg/m² basis) showed digital anomalies consisting of reduction in size and degree of ossification of the terminal phalanges in the fetuses. The frequency and severity of the changes appeared dose-related and were noted even at the lowest dose. These changes have been shown to occur with other members of the dihydropyridine class and are possibly a result of compromised uterine blood flow. Similar fetal anomalies were not observed in rats given felodipine.

In a teratology study in cynomolgus monkeys no reduction in the size of the terminal phalanges was observed but an abnormal position of the distal phalanges was noted in about 40 percent of the fetuses.

Nonteratogenic Effects: A prolongation of parturition with difficult labor and an increased frequency of fetal and early postnatal deaths were observed in rats administered doses of 9.6 mg/kg/day (4 times' the maximum human dose on a mg/m² basis) and above.

Significant enlargement of the mammary glands in excess of the normal enlargement for pregnant rabbits was found with doses greater than or equal to 1.2 mg/kg/day (equal to the maximum human dose on a mg/m² basis). This effect occurred only in pregnant rabbits and regressed during lactation. Similar changes in the mammary glands were not observed in rats or monkeys.

There are no adequate and well-controlled studies in pregnant women. If felodipine is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus, possible digital anomalies of the infant, and the potential effects of felodipine on labor and delivery, and on the mammary glands of pregnant females.

Nursing Mothers

It is not known whether this drug is secreted in human milk and because of the potential for serious adverse reactions from felodipine in the infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

In controlled studies in the United States and overseas approximately 3000 patients were treated with felodipine as either the extended-release or the immediate-release formulation.

The most common clinical adverse experiences reported with PLENDIL® (Felodipine) administered as monotherapy in all settings and with all dosage forms of felodipine were peripheral edema and headache. Peripheral edema was generally mild, but it was age- and dose-related and resulted in discontinuation of therapy in about 4 percent of the enrolled patients. Discontinuation of therapy due to any clinical adverse experience occurred in about 9 percent of the patients receiving PLENDIL, principally for peripheral edema, headache, or flushing.

Adverse experiences that occurred with an incidence of 1.5 percent or greater during monotherapy with PLENDIL without regard to causality are compared to placebo in the table below.

Percent of Patients with Adverse Effects in Controlled Trials of PLENDIL as Monotherapy (incidence of discontinuations shown in parentheses)

Adverse Effect	PLENDIL% N = 730	Placebo % N = 283
Peripheral Edema	22.3 (4.2)	3.5
Headache	18.6 (2.1)	10.6
Flushing	6.4 (1.0)	1.1
Dizziness	5.8 (0.8)	3.2
Upper Respiratory Infection	5.5 (0.1)	1.1
Asthenia	4.7 (0.1)	2.8
Cough	2.9 (0.0)	0.4
Paresthesia	2.5 (0.1)	1.8
Dyspepsia	2.3 (0.0)	1.4
Chest Pain	2.1 (0.1)	1.4
Nausea	1.9 (0.8)	1.1
Muscle Cramps	1.9 (0.0)	1.1
Palpitation	1.8 (0.5)	2.5
Abdominal Pain	1.8 (0.3)	1.1
Constipation	1.6 (0.1)	1.1
Diarrhea	1.6 (0.1)	1.1
Pharyngitis	1.6 (0.0)	0.4
Rhinorrhea	1.6 (0.0)	0.0
Back Pain	1.6 (0.0)	1.1
Rash	1.5 (0.1)	1.1

In the two dose response studies using PLENDIL® (Felodipine) as monotherapy, the following table describes the incidence (percent) of adverse experiences that were dose-related. The incidence of discontinuations due to these adverse experiences are shown in parentheses.

Adverse Effect	Placebo N = 121	2.5 mg N = 71	5.0 mg N = 72	10.0 mg N = 123	20 mg N = 50
Peripheral Edema	2.5 (1.6)	1.4 (0.0)	13.9 (2.8)	19.5 (2.4)	36.0 (10.0)
Palpitation	0.8 (0.8)	1.4 (0.0)	0.0 (0.0)	2.4 (0.8)	12.0 (8.0)
Headache	12.4 (0.0)	11.3 (1.4)	11.1 (0.0)	18.7 (4.1)	28.0 (18.0)
Flushing	0.0 (0.0)	4.2 (0.0)	2.8 (0.0)	8.1 (0.8)	20.0 (8.0)

In addition, adverse experiences that occurred in 0.5 up to 1.5 percent of patients who received PLENDIL in all controlled clinical studies (listed in order of decreasing severity within each category) and serious adverse events that occurred at a lower rate or were found during marketing experience (those lower rate events are in italics) were: *Body as a Whole:* Facial edema, warm sensation; *Cardiovascular:* Tachycardia, *myocardial infarction, hypotension, syncope, angina pectoris,* arrhythmia; *Digestive:* Vomiting, dry mouth, flatulence; *Hematologic: Anemia; Musculoskeletal:* Arthralgia, arm pain, knee pain, leg pain, foot pain, hip pain, myalgia; *Nervous/Psychiatric:* Depression, anxiety disorders, insomnia, irritability, nervousness, somnolence; *Respiratory:* Bronchitis, influenza, sinusitis, dyspnea, epistaxis, respiratory infection, sneezing; *Skin:* Contusion, erythema, urticaria; *Urogenital:* Decreased libido, impotence, urinary frequency, urinary urgency, dysuria.

Felodipine, as an immediate release formulation, has also been studied as monotherapy in 680 patients with hypertension in U.S. and overseas controlled clinical studies. Other adverse experiences not listed above and with an incidence of 0.5 percent or greater include: *Body as a Whole:* Fatigue; *Digestive:* Gastrointestinal pain; *Musculoskeletal:* Arthritis, local weakness, neck pain, shoulder pain, ankle pain; *Nervous/Psychiatric:* Tremor; *Respiratory:* Rhinitis; *Skin:* Hyperhidrosis, pruritus; *Special Senses:* Blurred vision, tinnitus; *Urogenital:* Nocturia.

Gingival Hyperplasia: Gingival hyperplasia, usually mild, occurred in <0.5 percent of patients in controlled studies. This condition may be avoided or may regress with improved dental hygiene. (See PRECAUTIONS, *Information for Patients.*)

Clinical Laboratory Test Findings

Serum Electrolytes: No significant effects on serum electrolytes were observed during short- and long-term therapy.

Serum Glucose: No significant effects on fasting serum glucose were observed in patients treated with PLENDIL in the U.S. controlled study.

Liver Enzymes: One of two episodes of elevated serum transaminases decreased once drug was discontinued in clinical studies; no follow-up was available for the other patient.

OVERDOSAGE

Oral doses of 240 mg/kg and 264 mg/kg in male and female mice, respectively and 2390 mg/kg and 2250 mg/kg in male and female rats, respectively, caused significant lethality.

In a suicide attempt, one patient took 150 mg felodipine together with 15 tablets each of atenolol and spironolactone and 20 tablets of nitrazepam. The patient's blood pressure and heart rate were normal on admission to hospital; he subsequently recovered without significant sequelae.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly bradycardia.

If severe hypotension occurs, symptomatic treatment should be instituted. The patient should be placed supine with the legs elevated. The administration of intravenous fluids may be useful to treat hypotension due to overdosage with calcium antagonists. In case of accompanying bradycardia, atropine (0.5-1 mg) should be administered intravenously. Sympathomimetic drugs may also be given if the physician feels they are warranted.

It has not been established whether felodipine can be removed from the circulation by hemodialysis.

DOSAGE AND ADMINISTRATION

The recommended initial dose is 5 mg once a day. Therapy should be adjusted individually according to patient response, generally at intervals of not less than two weeks. The usual dosage range is 5-10 mg once daily. The maximum recommended daily dose is 20 mg once a day. That dose in clinical trials showed an increased blood pressure response but a large increase in the rate of peripheral edema and other vasodilatory adverse events (see ADVERSE REACTIONS). Modification of the recommended dosage is usually not required in patients with renal impairment.

PLENDIL should be swallowed whole and not crushed or chewed.

Use in the Elderly or Patients with Impaired Liver Function: Patients over 65 years of age or patients with impaired liver function, because they may develop higher plasma concentrations of felodipine, should have their blood pressure monitored closely during dosage adjustment (see PRECAUTIONS). In general, doses above 10 mg should not be considered in these patients.

[redacted]

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For more detailed information, consult your Astra/Merck Specialist or see complete Prescribing Information.

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†Based on patient weight of 50 kg

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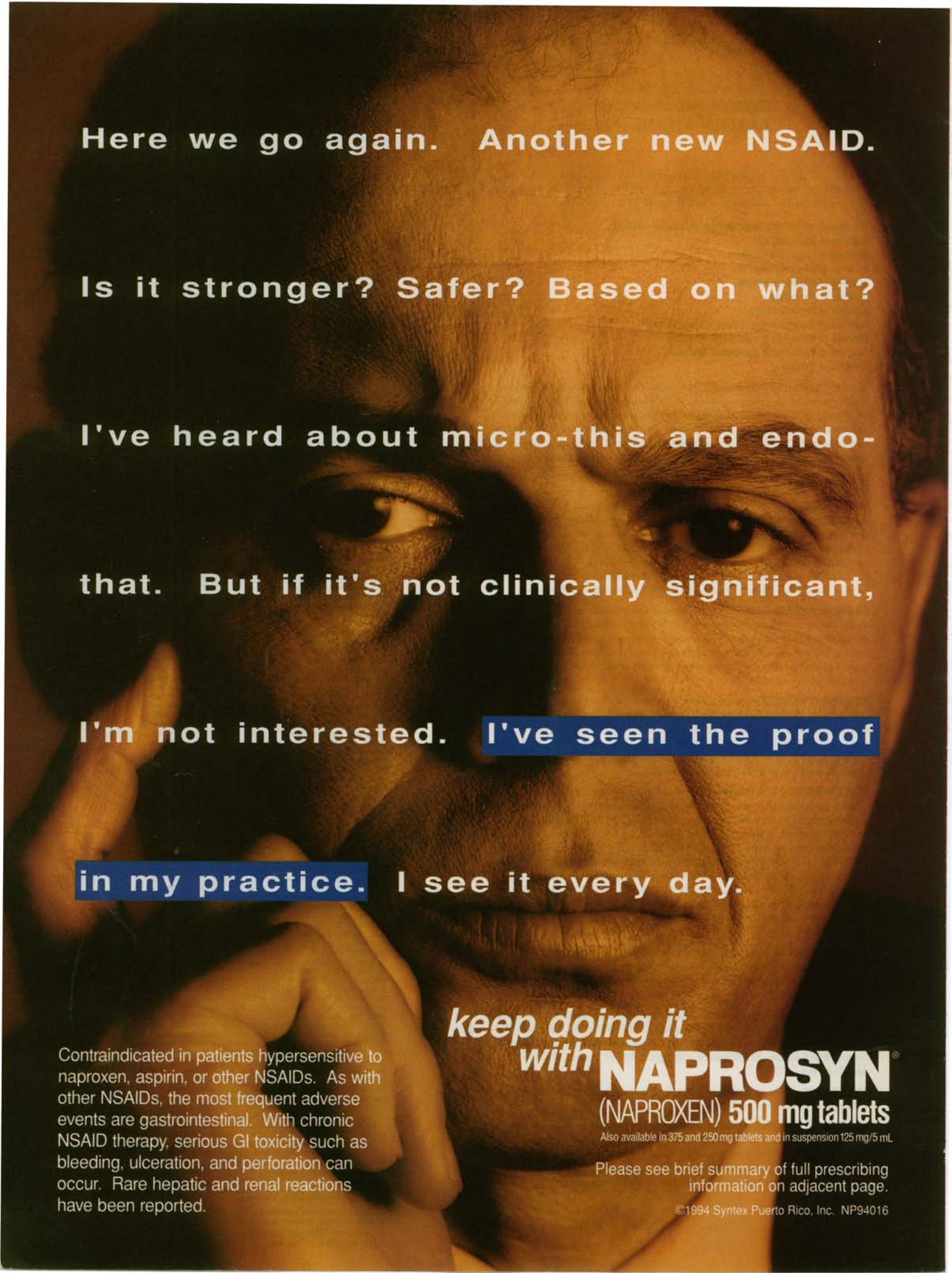
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VOL 3 NO. 2, FEB 1994

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(verapamil HCl)

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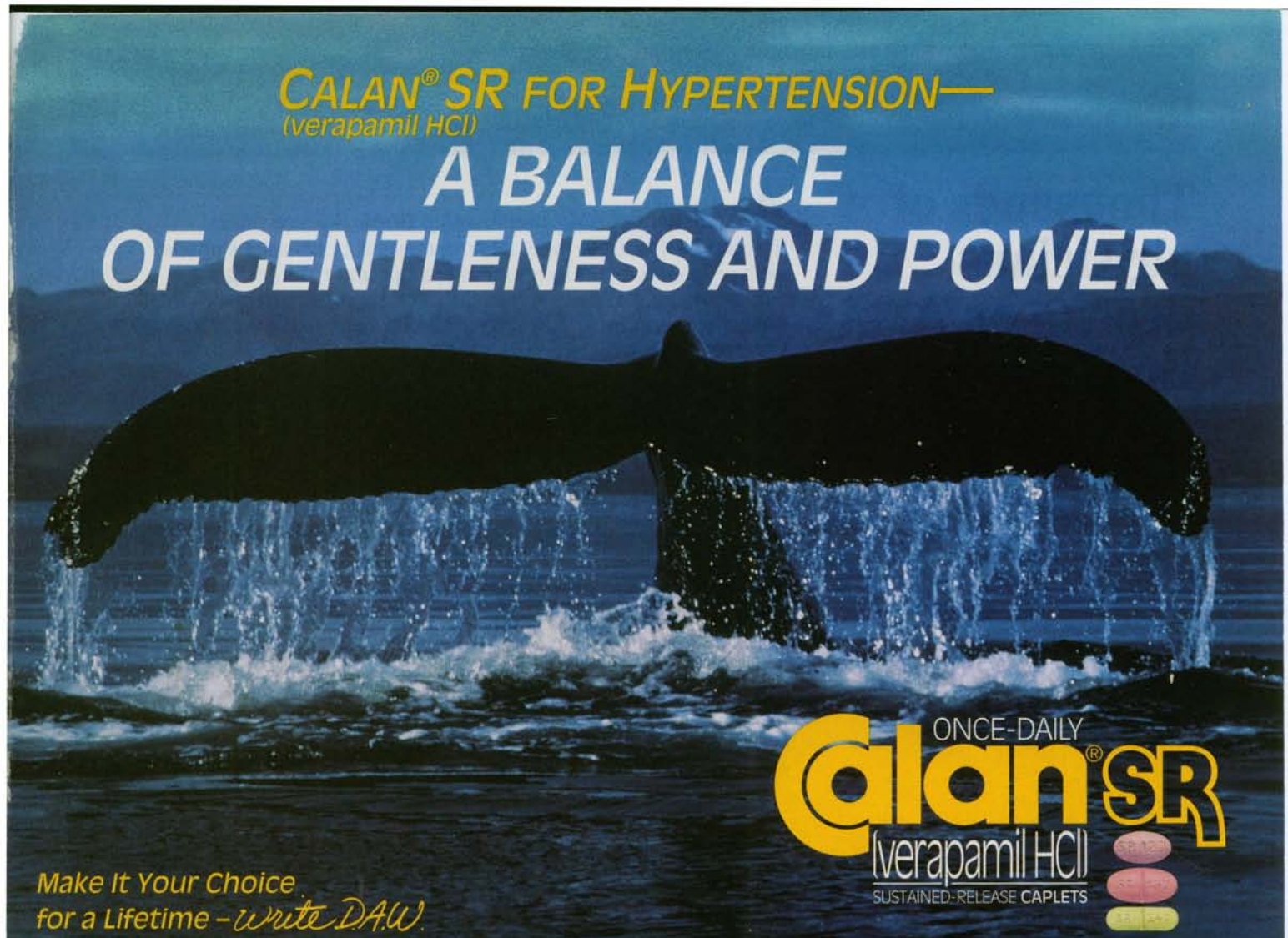

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The recommended starting dosage for Calan SR is 180 mg once daily. Dose titration will be required in some patients to achieve blood pressure control. A lower starting dosage of 120 mg/day may be warranted in some patients (eg, the elderly, patients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

BRIEF SUMMARY

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

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

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

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

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Sugar Free

Expectorant vicodin TUSS™ C III Dual Action Cough Therapy

New

Expectorant

vicodin TUSS™ III

(hydrocodone bitartrate 5mg (Warning: May be habit forming) and guaifenesin 100mg per (5mL) teaspoon)

Combines the antitussive action of hydrocodone with the expectorant action of guaifenesin.

- Hydrocodone helps suppress dry, hacking coughs for up to 6 hours.
- Guaifenesin enables those coughs that do occur to be more productive.
- Long lasting relief in a sugar-free, alcohol-free, dye-free, cherry flavored formula.
- Adult Dose: 1 teaspoon (5mL) every 4-6 hours not to exceed 6 teaspoons in a 24 hour period.

New

Expectorant

vicodin TUSS™ III

(hydrocodone bitartrate 5mg (Warning: May be habit forming) and guaifenesin 100mg per (5mL) teaspoon)

Alcohol Free

Sugar Free

Effective cough relief you can phone in.

INDICATIONS AND USAGE: VICODIN TUSS™ Expectorant is indicated for the symptomatic relief of irritating non-productive cough associated with upper and lower respiratory tract congestion. **CONTRAINDICATIONS:** VICODIN TUSS™ Expectorant is contraindicated in patients hypersensitive to hydrocodone or guaifenesin. Patients known to be hypersensitive to other opioids may exhibit cross sensitivity to VICODIN TUSS™ Expectorant. Hydrocodone is contraindicated in the presence of an intracranial lesion associated with increased intracranial pressure; and whenever ventilatory function is depressed. **WARNINGS:** May be habit forming. Hydrocodone can produce drug dependence of the morphine type and therefore has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of VICODIN TUSS™ Expectorant and it should be prescribed and administered with the same degree of caution appropriate to the use of other narcotic drugs (see DRUG ABUSE AND DEPENDENCE). **Respiratory Depression:** VICODIN TUSS™ Expectorant produces dose-related respiratory depression by directly acting on the brain stem respiratory centers. If respiratory depression occurs, it may be antagonized by the use of naloxone hydrochloride and other supportive measures when indicated. **Head Injury and Increased Intracranial Pressure:** The respiratory depressant properties of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries. **Acute Abdominal Conditions:** The administration of VICODIN TUSS™ Expectorant or other opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions. **PRECAUTIONS:** Before prescribing medication to suppress or modify cough, it is important to ascertain that the underlying cause of cough is identified, that modification of cough does not increase the risk of clinical or physiologic complications, and that appropriate therapy for the primary disease is provided. **Usage in Ambulatory Patients:** Hydrocodone, like all narcotics, may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, and patients should be warned accordingly. **Drug Interactions:** Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative hypnotics or other CNS depressants (including alcohol) concomitantly with hydrocodone may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced (see WARNINGS). **Laboratory Interactions:** The metabolite of guaifenesin has been found to produce an apparent increase in urinary 5-hydroxyindoleacetic acid, and guaifenesin therefore may interfere with the interpretation of this test for the diagnosis of carcinoid syndrome. Guaifenesin administration should be discontinued 24 hours prior to the collection of urine specimens for the determination of 5-hydroxyindoleacetic acid. **Carcinogenesis, mutagenesis, impairment of fertility:** Carcinogenicity, mutagenicity and reproduction studies have not been conducted with VICODIN TUSS™ Expectorant. **Usage in Pregnancy:** Pregnancy Category C. Animal reproduction studies have not been conducted with VICODIN TUSS™ Expectorant. It is also not known whether VICODIN TUSS™ Expectorant can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. VICODIN TUSS™ Expectorant should be given to a pregnant woman only if clearly needed. **Nonteratogenic effects:** Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal. Chlorpromazine 0.7-1.0 mg/kg q 6 h, phenobarbital 2 mg/kg q 6 h, and paregoric 2-4 drops/kg q 4 h, have been used to treat withdrawal symptoms in infants. The duration of therapy is 4 to 28 days, with the dosages decreased as tolerated. **Nursing mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from VICODIN TUSS™ Expectorant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. **ADVERSE REACTIONS Respiratory System:** Hydrocodone produces dose-related respiratory depression by acting directly on brain stem respiratory centers. **Cardiovascular System:** Hypertension, postural hypotension and palpitations. **Genitourinary System:** Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates. **Central Nervous System:** Sedation, drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, dizziness, psychic dependence, mood changes and blurred vision. **Gastrointestinal System:** Nausea and vomiting occur more frequently in ambulatory than in recumbent patients. **DRUG ABUSE AND DEPENDENCE:** Special care should be exercised in prescribing hydrocodone for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. VICODIN TUSS™ Expectorant is a Schedule III narcotic. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of narcotics; therefore, VICODIN TUSS™ Expectorant should always be prescribed and administered with caution. Physical dependence is the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome. Patients physically dependent on opioids will develop an abstinence syndrome upon abrupt discontinuation of the opioid or following the administration of a narcotic antagonist. The character and severity of the withdrawal symptoms are related to the degree of physical dependence. Manifestations of opioid withdrawal are similar to but milder than that of morphine and include lacrimation, rhinorrhea, yawning, sweating, restlessness, dilated pupils, anorexia, goose-flesh, irritability, and tremor. In more severe forms, nausea, vomiting, intestinal spasm and diarrhea, increased heart rate and blood pressure, chills, and pains in bones and muscles of the back and extremities may occur. Peak effects will usually be apparent at 48 to 72 hours. Treatment of withdrawal is usually managed by providing sufficient quantities of an opioid to suppress **severe** withdrawal symptoms and then gradually reducing the dose of opioid over a period of several days. **OVERDOSAGE: Signs and Symptoms:** Serious overdosage with VICODIN TUSS™ Expectorant is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage apnea, circulatory collapse, cardiac arrest, and death may occur. **Treatment:** Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist naloxone hydrochloride is a specific antidote for respiratory depression which may result from overdosage or unusual sensitivity to narcotics including hydrocodone. Therefore, an appropriate dose of naloxone hydrochloride should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. For further information, see full prescribing information for naloxone hydrochloride. An antagonist should not be administered in the absence of clinically significant respiratory depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated. Gastric emptying may be useful in removing unabsorbed drug. Activated charcoal may be of benefit.

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

knoll

BASF Group

V3110/7-93

Printed In U.S.A.

LOZOL® 1.25 MG
INDAPAMIDE TABLETS

Antihypertensive Efficacy Equivalent to 2.5 mg[1*]

With the benefits of a lower once-daily dose

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

Safe and effective for step-down therapy

Side-effect profile compatible with other antihypertensive agents

LOZOL 1.25 mg once daily is now the recommended starting dose for indapamide

LOZOL 1.25 MG. A LITTLE MEANS A LOT.

** In a controlled clinical trial at 16 weeks, the changes in supine diastolic and systolic BPs with 1.25 mg of indapamide were not statistically different from LOZOL 2.5 mg.*

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

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

Please see brief summary of prescribing information on this page.

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

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

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

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

PRECAUTIONS: Perform serum electrolyte determinations at appropriate intervals, especially in patients who are vomiting excessively or receiving parenteral fluids, in patients subject to electrolyte imbalance, or in patients on a salt-restricted diet. In addition, patients should be observed for clinical signs of fluid or electrolyte imbalance, such as hyponatremia, hypochloremic alkalosis, or hypokalemia. The risk of hypokalemia secondary to diuresis and natriuresis is increased with larger doses, with brisk diuresis, with severe cirrhosis, and with concomitant use of corticosteroids or ACTH. Interference with adequate oral intake of electrolytes will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis, such as increased ventricular irritability.
Dilutional hyponatremia may occur in edematous patients; appropriate treatment is usually water restriction. In actual salt depletion, appropriate replacement is the treatment of choice. Chloride deficit is usually mild, not requiring specific treatment except in extraordinary circumstances (liver, renal disease). Thiazide-like diuretics have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.
Hyperuricemia may occur, and frank gout may be precipitated in certain patients receiving indapamide. Serum concentrations of uric acid should be monitored periodically.
Use with caution in patients with severe renal disease; consider withholding or discontinuing if progressive renal impairment is observed. Renal function tests should be performed periodically.
Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
Latent diabetes may become manifest and insulin requirements in diabetic patients may be altered during thiazide administration. A mean increase in glucose of 6.47 mg/dL was observed in patients treated with indapamide 1.25 mg, which was not considered clinically significant in these trials. Serum concentrations of glucose should be monitored routinely during treatment with indapamide.
Calcium excretion is decreased by diuretics pharmacologically related to indapamide. After six to eight weeks of indapamide 1.25 mg treatment and in long-term studies of hypertensive patients with higher doses of indapamide, however, serum concentrations of calcium increased only slightly with indapamide. Indapamide may decrease serum PBI levels without signs of thyroid disturbance. Complications of hyperparathyroidism have not been seen. Discontinue before tests of parathyroid function are performed.
Thiazides have exacerbated or activated systemic lupus erythematosus. Consider this possibility with indapamide.

DRUG INTERACTIONS: LOZOL may add to or potentiate the action of other antihypertensive drugs. The antihypertensive effect of the drug may be enhanced in the postsympathectomized patient. Indapamide may decrease arterial responsiveness to norepinephrine, but this does not preclude the use of norepinephrine.
In mouse and rat lifetime carcinogenicity studies, there were no significant differences in the incidence of tumors between the indapamide-treated animals and the control groups.
Pregnancy Category B: Diuretics cross the placental barrier and appear in cord blood. Indapamide should be used during pregnancy only if clearly needed. Use may be associated with fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse effects that have occurred in adults. It is not known whether this drug is excreted in human milk. If use of this drug is deemed essential, the patient should stop nursing.

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

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.
Keep tightly closed. Store at controlled room temperature, 15°-30°C (59°-86°F). Avoid excessive heat. Dispense in tight containers as defined in USP.
See product circular for full prescribing information.
Revised: 5/93

Reference: 1. Data on file, Rhône-Poulenc Rorer Pharmaceuticals Inc.
Product of Servier Research Institute

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

FC#94-R18

NOW FOR ANGINA

THE ONE

CARDIZEM® CD

(diltiazem HCl) 120-, 180-, 240-, 300-mg Capsules

PROVEN 24-HOUR CONTROL OF BOTH ANGINA AND HYPERTENSION[1,2]

Please see brief summary of prescribing information on adjacent page.

0115A3

ONCE-A-DAY CARDIZEM® CD

(diltiazem HCl)

24-HOUR CONTROL OF BOTH ANGINA AND HYPERTENSION

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

CARDIZEM® CD (diltiazem HCl)

Capsules

CONTRAINDICATIONS

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

WARNINGS

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

PRECAUTIONS

General

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

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

Drug Interactions

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

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

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

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

Cimetidine. A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1200 mg per day and a single dose of diltiazem 60 mg. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

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

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

Available as Once-A-Day

120-mg capsules

180-mg capsules

240-mg capsules

300-mg capsules

℞ Cardizem CD Start with one 180-mg capsule daily

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Pregnancy

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

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

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

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

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

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

CARDIZEM CD Capsule Placebo-Controlled Angina and Hypertension Trials Combined

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

In clinical trials of CARDIZEM CD Capsules, CARDIZEM Tablets, and CARDIZEM SR Capsules involving over 3200 patients, the most common events (ie, greater than 1%) were edema (4.6%), headache (4.6%), dizziness (3.5%), asthenia (2.6%), first-degree AV block (2.4%), bradycardia (1.7%), flushing (1.4%), nausea (1.4%), and rash (1.2%).

In addition, the following events were reported infrequently (less than 1%) in angina or hypertension trials:

Cardiovascular: Angina, arrhythmia, AV block (second- or third-degree), bundle branch block, congestive heart failure, ECG abnormalities, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor

Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeusia, dyspepsia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hepatic warnings), thirst, vomiting, weight increase

Dermatological: Petechiae, photosensitivity, pruritus, urticaria

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, erythema multiforme, exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well-documented cases of generalized rash, characterized as leukocytoclastic vasculitis, have been reported.

However, a definitive cause and effect relationship between these events and CARDIZEM therapy is yet to be established.

Prescribing Information as of October 1992 (2)

Marion Merrell Dow Inc.
Kansas City, MO 64114

ccdb1092(2)a

References: 1. Data on file, Marion Merrell Dow Inc. **2.** Massie BM, Der E, Herman TS, Topolski P, Park GD, Stewart WH. *Clin Cardiol.* 1992;15:365-368.

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

NEW LODINE® 400mg
ETODOLAC TABLETS

Extra Strength, 400 mg, That Works In Osteoarthritis

Simple B.I.D. Choice*

Same Favorable LODINE Tolerability†

NEW LODINE® 400mg
ETODOLAC TABLETS

More Strength To Live With Osteoarthritis

* Recommended starting dosage in OA is 800 mg to 1,200 mg/day in divided doses.

† 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.

63848N

Please see adjacent page for brief summary of prescribing information.

Be on the inside of health system reform

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Join us and make a difference

Partnership in Action: Uniting for America's Health

When reform proposals take shape, will your views be included? Specific health reform proposals are being hammered into policy in our nation's capital. Now is the time to ask questions and voice concerns.

The American Medical Association will host an interactive meeting of key congressional policy makers and physicians from across the country. *Partnership in Action: Uniting for America's Health* takes place March 8 in Washington, DC.

March 8 will be a day filled with interactive dialogue between policy makers and the physicians who will be affected by those policies. Dinners will feature roundtable discussions with congressional members from coast to coast.

Your presence at the 1994 summit can make a difference. To register now, call 800 262-3211.

American Medical Association

Physicians dedicated to the health of America

TAKE EFFECTIVE CONTROL OF BED-WETTING

- Rapid response–substantial effect seen in as little as 1 to 3 nights of therapy[1]
- A combined 15-year record of successful and safe use in the U.S. and Europe[2]
- May be used hand in hand with behavior modification

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 adjacent 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. Aladjem M, Wohl R, Boichis H, et al: Desmopressin in nocturnal enuresis. *Arch Dis Child* 1982;57:137-140.
2. Bloom DA: The American experience with desmopressin. *Clin Pediatr* 1993(July, special edition):28-31.

Manufactured for
RHÔNE-POULENC RORER
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The First in a New Chemical Class of Non-benzodiazepine Sleep Agents

AMBIEN™
(ZOLPIDEM TARTRATE) C IV
5-MG & 10-MG TABLETS

- AMBIEN—an imidazopyridine, chemically unrelated to benzodiazepines or any other sleep agent
- AMBIEN—indicated for short-term management of insomnia (generally limited to 7 to 10 days)
- A low incidence of adverse events

  In short-term treatment (up to 10 nights) with AMBIEN at doses ≤ 10 mg, the adverse events seen at statistically significant differences from placebo were: drowsiness (2%), dizziness (1%), and diarrhea (1%); and in longer-term treatment (28 to 35 nights): dizziness (5%) and drugged feelings (3%).
- Extensive clinical experience—over 500 million doses prescribed throughout Europe[1]
- Generally preserves normal sleep physiology (clinical significance unknown)
- A short half-life — mean 2.5 hours, with no active metabolites

SEARLE

1. Data on file.

Please see adjacent page for brief summary of prescribing information.

Ambien™ C-IV
(zolpidem tartrate)

BRIEF SUMMARY

INDICATIONS AND USAGE

Ambien (zolpidem tartrate) is indicated for the short-term treatment of insomnia. Hypnotics should generally be limited to 7 to 10 days of use, and reevaluation of the patient is recommended if they are to be taken for more than 2 to 3 weeks.

Ambien should not be prescribed in quantities exceeding a 1-month supply (see *Warnings*).

CONTRAINDICATIONS

None known.

WARNINGS

Since sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness which should be evaluated. Worsening of insomnia or the emergence of new thinking or behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative/hypnotic drugs, including Ambien. Because some of the important adverse effects of Ambien appear to be dose related (see *Precautions* and *Dosage and Administration*), it is important to use the smallest possible effective dose, especially in the elderly.

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative/hypnotics. Some of these changes may be characterized by decreased inhibition (eg, aggressiveness and extroversion that seemed out of character), similar to effects produced by alcohol and other CNS depressants. Other reported behavioral changes have included bizarre behavior, agitation, hallucinations, and depersonalization. Amnesia and other neuropsychiatric symptoms may occur unpredictably. In primarily depressed patients, worsening of depression, including suicidal thinking, has been reported in association with the use of sedative/hypnotics.

It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above are drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

Following the rapid dose decrease or abrupt discontinuation of sedative/hypnotics, there have been reports of signs and symptoms similar to those associated with withdrawal from other CNS-depressant drugs (see *Drug Abuse and Dependence*).

Ambien, like other sedative/hypnotic drugs, has CNS-depressant effects. Due to the rapid onset of action, Ambien should only be ingested immediately prior to going to bed. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination such as operating machinery or driving a motor vehicle after ingesting the drug, including potential impairment of the performance of such activities that may occur the day following ingestion of Ambien. Ambien showed additive effects when combined with alcohol and should not be taken with alcohol. Patients should also be cautioned about possible combined effects with other CNS-depressant drugs. Dosage adjustments may be necessary when Ambien is administered with such agents because of the potentially additive effects.

PRECAUTIONS

General

Use in the elderly and/or debilitated patients: Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative/hypnotic drugs is a concern in the treatment of elderly and/or debilitated patients. Therefore, the recommended Ambien dosage is 5 mg in such patients (see *Dosage and Administration*) to decrease the possibility of side effects. These patients should be closely monitored.

Use in patients with concomitant illness: Clinical experience with Ambien in patients with concomitant systemic illness is limited. Caution is advisable in using Ambien in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Although preliminary studies did not reveal respiratory depressant effects at hypnotic doses of Ambien in normals, precautions should be observed if Ambien is prescribed to patients with compromised respiratory function, since sedative/hypnotics have the capacity to depress respiratory drive. Data in end-stage renal failure patients repeatedly treated with Ambien did not demonstrate drug accumulation or alterations in pharmacokinetic parameters. No dosage adjustment in renally impaired patients is required; however, these patients should be closely monitored (see *Pharmacokinetics*). A study in subjects with hepatic impairment did reveal prolonged elimination in this group; therefore, treatment should be initiated with 5 mg in patients with hepatic compromise, and they should be closely monitored.

Use in depression: As with other sedative/hypnotic drugs, Ambien should be administered with caution to patients exhibiting signs or symptoms of depression. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional overdosage is more common in this group of patients; therefore, the least amount of drug that is feasible should be prescribed for the patient at any one time.

Information for patients: Patient information is printed in the complete prescribing information and is available in pads for distribution to patients.

Laboratory tests: There are no specific laboratory tests recommended.

Drug interactions

CNS-active drugs: Ambien was evaluated in healthy volunteers in single-dose interaction studies for several CNS drugs. A study involving haloperidol and zolpidem revealed no effect of haloperidol on the pharmacokinetics or pharmacodynamics of zolpidem. Imipramine in combination with zolpidem produced no pharmacokinetic interaction other than a 20% decrease in peak levels of imipramine, but there was an additive effect of decreased alertness. Similarly, chlorpromazine in combination with zolpidem produced no pharmacokinetic interaction, but there was an additive effect of decreased alertness and psychomotor performance. The lack of a drug interaction following single-dose administration does not predict a lack following chronic administration.

An additive effect on psychomotor performance between alcohol and zolpidem was demonstrated.

Since the systematic evaluations of Ambien in combination with other CNS-active drugs have been limited, careful consideration should be given to the pharmacology of any CNS-active drug to be used with zolpidem. Any drug with CNS-depressant effects could potentially enhance the CNS-depressant effects of zolpidem.

Other drugs: A study involving cimetidine/zolpidem and ranitidine/zolpidem combinations revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of zolpidem. Zolpidem had no effect on digoxin kinetics and did not affect prothrombin time when given with warfarin in normal subjects. Zolpidem's sedative/hypnotic effect was reversed by flumazenil; however, no significant alterations in zolpidem pharmacokinetics were found.

Drug/Laboratory test interactions: Zolpidem is not known to interfere with commonly employed clinical laboratory tests.

Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenesis: Zolpidem was administered to rats and mice for 2 years at dietary dosages of 4, 18, and 80 mg/kg/day. In mice, these doses are 26 to 520 times or 2 to 35 times the maximum 10-mg human dose on a mg/kg or mg/m² basis, respectively. In rats these doses are 43 to 876 times or 6 to 115 times the maximum 10-mg human dose on a mg/kg or mg/m² basis, respectively. No evidence of carcinogenic potential was observed in mice. Renal liposarcomas were seen in 4/100 rats (3 males, 1 female) receiving 80 mg/kg/day and a renal lipoma was observed in one male rat at the 18 mg/kg/day dose. Incidence rates of lipoma and liposarcoma for zolpidem were comparable to those seen in historical controls and the tumor findings are thought to be a spontaneous occurrence.

Mutagenesis: Zolpidem did not have mutagenic activity in several tests including the Ames test, genotoxicity in mouse lymphoma cells in vitro, chromosomal aberrations in cultured human lymphocytes, unscheduled DNA synthesis in rat hepatocytes in vitro, and the micronucleus test in mice.

Impairment of fertility: In a rat reproduction study, the high dose (100 mg base/kg) of zolpidem resulted in irregular estrus cycles and prolonged precoital intervals, but there was no effect on male or female fertility after daily oral doses of 4 to 100 mg base/kg or 5 to 130 times the recommended human dose in mg/m². No effects on any other fertility parameters were noted.

Pregnancy

Category B. Studies to assess the effects of zolpidem on human reproduction and development have not been conducted.

Teratology studies were conducted in rats and rabbits.

In rats, adverse maternal and fetal effects occurred at 20 and 100 mg base/kg and included dose-related maternal lethargy and ataxia and a dose-related trend to incomplete ossification of fetal skull bones.

In rabbits, dose-related maternal sedation and decreased weight gain occurred at all doses tested. At the high dose, 16 mg base/kg, there was an increase in postimplantation fetal loss and underossification of sternebrae in viable fetuses.

This drug should be used during pregnancy only if clearly needed.

Nonteratogenic effects: Studies to assess the effects on children whose mothers took zolpidem during pregnancy have not been conducted. However, children born of mothers taking sedative/hypnotic drugs may be at some risk for withdrawal symptoms from the drug during the postnatal period. In addition, neonatal flaccidity has been reported in infants born of mothers who received sedative/hypnotic drugs during pregnancy.

Labor and delivery: Ambien has no established use in labor and delivery.

Nursing mothers: Studies in lactating mothers indicate that between 0.004 and 0.019% of the total administered dose is excreted into milk, but the effect of zolpidem on the infant is unknown.

The use of Ambien in nursing mothers is not recommended.

Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS

Associated with discontinuation of treatment: Approximately 4% of 1,701 patients who received zolpidem at all doses (1.25 to 90 mg) in U.S. premarketing clinical trials discontinued treatment because of an adverse clinical event. Events most commonly associated with discontinuation from U.S. trials were daytime drowsiness (0.5%), dizziness (0.4%), headache (0.5%), nausea (0.6%), and vomiting (0.5%).

Approximately 6% of 1,320 patients who received zolpidem at all doses (5 to 50 mg) in similar foreign trials discontinued treatment because of an adverse event. Events most commonly associated with discontinuation from these trials were daytime drowsiness (1.6%), amnesia (0.6%), dizziness (0.6%), headache (0.6%), and nausea (0.6%).

Incidence in controlled clinical trials

Most commonly observed adverse events in controlled trials: During short-term treatment (up to 10 nights) with Ambien at doses up to 10 mg, the most commonly observed adverse events associated with the use of zolpidem and seen at statistically significant differences from placebo-treated patients were drowsiness (reported by 2% of zolpidem patients), dizziness (1%), and diarrhea (1%). During longer-term treatment (28 to 35 nights) with zolpidem at doses up to 10 mg, the most commonly observed adverse events associated with the use of zolpidem and seen at statistically significant differences from placebo-treated patients were dizziness (5%) and drugged feelings (3%).

Incidence of Treatment-Emergent Adverse Experiences in Short-term Placebo-Controlled Clinical Trials
(Percentage of patients reporting)

Body System/ Adverse Event*	Zolpidem (≤10 mg) (N=685)	Placebo (N=473)
Central and Peripheral Nervous System		
Headache	7	6
Drowsiness	2	–
Dizziness	1	–
Gastrointestinal System		
Nausea	2	3
Diarrhea	1	–
Musculoskeletal System		
Myalgia	1	2

*Events reported by at least 1% of Ambien patients are included.

Incidence of Treatment-Emergent Adverse Experiences in Long-term Placebo-Controlled Clinical Trials
(Percentage of patients reporting)

Body System/ Adverse Event*	Zolpidem (≤10 mg) (N=152)	Placebo (N=161)
Autonomic Nervous System		
Dry mouth	3	1
Body as a Whole		
Allergy	4	1
Back pain	3	2
Influenza-like symptoms	2	–
Chest pain	1	–
Fatigue	1	2
Cardiovascular System		
Palpitation	2	–
Central and Peripheral Nervous System		
Headache	19	22
Drowsiness	8	5
Dizziness	5	1
Lethargy	3	1
Drugged feeling	3	–
Lightheadedness	2	1
Depression	2	1
Abnormal dreams	1	–
Amnesia	1	–
Anxiety	1	1
Nervousness	1	3
Sleep disorder	1	–
Gastrointestinal System		
Nausea	6	6
Dyspepsia	5	6
Diarrhea	3	2
Abdominal pain	2	2
Constipation	2	1
Anorexia	1	1
Vomiting	1	1
Immunologic System		
Infection	1	1

Incidence of Treatment-Emergent Adverse Experiences in Long-term Placebo-Controlled Clinical Trials (Cont'd)
(Percentage of patients reporting)

Body System/ Adverse Event*	Zolpidem (≤10 mg) (N=152)	Placebo (N=161)
Musculoskeletal System		
Myalgia	7	7
Arthralgia	4	4
Respiratory System		
Upper respiratory infection	5	6
Sinusitis	4	2
Pharyngitis	3	1
Rhinitis	1	3
Skin and Appendages		
Rash	2	1
Urogenital System		
Urinary tract infection	2	2

*Events reported by at least 1% of patients treated with Ambien.

There is evidence from dose comparison trials suggesting a dose relationship for many of the adverse events associated with zolpidem use, particularly for certain CNS and gastrointestinal adverse events.

Adverse events are further classified and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in greater than 1/100 subjects; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Frequent: abdominal pain, amnesia, ataxia, confusion, depression, diarrhea, diplopia, dizziness, dreaming abnormal, drowsiness, drugged feeling, dry mouth, dyspepsia, euphoria, fatigue, headache, insomnia, lethargy, lightheadedness, myalgia, nausea, upper respiratory infection, vertigo, vision abnormal, vomiting.

Infrequent: agitation, allergy, anorexia, anxiety, arthralgia, arthritis, asthenia, back pain, bronchitis, cerebrovascular disorder, chest pain, constipation, coughing, cystitis, decreased cognition, detached, difficulty concentrating, dysarthria, dysphagia, dyspnea, edema, emotional lability, eye irritation, falling, fever, flatulence, gastroenteritis, hallucination, hiccup, hyperglycemia, hypertension, hypoaesthesia, infection, influenza-like symptoms, malaise, menstrual disorder, migraine, nervousness, pallor, palpitation, paresthesia, pharyngitis, postural hypotension, pruritus, rash, rhinitis, scleritis, SGPT increased, sinusitis, sleep disorder, sleeping (after daytime dosing), stupor, sweating increased, tachycardia, taste perversion, tinnitus, tooth disorder, trauma, tremor, urinary incontinence, urinary tract infection, vaginitis.

Rare: abdominal body sensation, abscess, acne, acute renal failure, aggressive reaction, allergic reaction, allergy aggravated, anaphylactic shock, anemia, appetite increased, arrhythmia, arteritis, arthrosis, bilirubinemia, breast fibroadenosis, breast neoplasm, breast pain female, bronchospasm, bullous eruption, BUN increased, circulatory failure, corneal ulceration, delusion, dementia, depersonalization, dermatitis, dysphasia, dysuria, edema periorbital, enteritis, epistaxis, eructation, esophagospasm, ESR increased, extrasystoles, eye pain, face edema, feeling strange, flushing, furunculosis, gastritis, glaucoma, gout, hemorrhoids, hepatic function abnormal, herpes simplex, herpes zoster, hot flashes, hypercholesteremia, hyperhemoglobinemia, hyperlipidemia, hypertension aggravated, hypotension, hypotonia, hypoxia, hysteria, illusion, impotence, injection site inflammation, intestinal obstruction, intoxicated feeling, lacrimation abnormal, laryngitis, leg cramps, leukopenia, libido decreased, lymphadenopathy, macrocytic anemia, manic reaction, micturition frequency, muscle weakness, myocardial infarction, neuralgia, neuritis, neuropathy, neurosis, otitis externa, otitis media, pain, panic attack, paresis, personality disorder, phlebitis, photopsia, photosensitivity reaction, pneumonia, polyuria, pulmonary edema, pulmonary embolism, purpura, pyelonephritis, rectal hemorrhage, renal pain, restless legs, rigors, saliva altered, sciatica, SGOT increased, somnambulism, suicide attempt, syncope, tendinitis, tenesmus, tetany, thinking abnormal, thirst, tolerance increased, tooth caries, urinary retention, urticaria, varicose veins, ventricular tachycardia, weight decrease, yawning.

DRUG ABUSE AND DEPENDENCE

Controlled substance: Schedule IV.

Abuse and dependence: Studies of abuse potential in former drug abusers found that the effects of single doses of zolpidem tartrate 40 mg were similar, but not identical, to diazepam 20 mg, while zolpidem tartrate 10 mg was difficult to distinguish from placebo.

Sedative/hypnotics have produced withdrawal signs and symptoms following abrupt discontinuation. These reported symptoms range from mild dysphoria and insomnia to a withdrawal syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors, and convulsions. The U.S. clinical trial experience from zolpidem does not reveal any clear evidence for withdrawal syndrome. Nevertheless, the following adverse events included in DSM-III-R criteria for uncomplicated sedative/hypnotic withdrawal were reported at an incidence of ≤1% during U.S. clinical trials following placebo substitution occurring within 48 hours following last zolpidem treatment: fatigue, nausea, flushing, lightheadedness, uncontrolled crying, emesis, stomach cramps, panic attack, nervousness, and abdominal discomfort.

Individuals with a history of addiction to, or abuse of, drugs or alcohol are at risk of habituation and dependence; they should be under careful surveillance when receiving any hypnotic.

OVERDOSAGE

Signs and symptoms: In European postmarketing reports of overdose with zolpidem alone, impairment of consciousness has ranged from somnolence to light coma, with one case each of cardiovascular and respiratory compromise. Individuals have fully recovered from zolpidem tartrate overdoses up to 400 mg (40 times the maximum recommended dose). Overdose cases involving multiple CNS-depressant agents, including zolpidem, have resulted in more severe symptomatology, including fatal outcomes.

Recommended treatment: General symptomatic and supportive measures should be used along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Flumazenil may be useful. Respiration, pulse, blood pressure, and other appropriate signs should be monitored and general supportive measures employed. Sedating drugs should be withheld following zolpidem overdosage. Zolpidem is not dialyzable.

The possibility of multiple drug ingestion should be considered.

Caution: Federal law prohibits dispensing without prescription.

5/27/93

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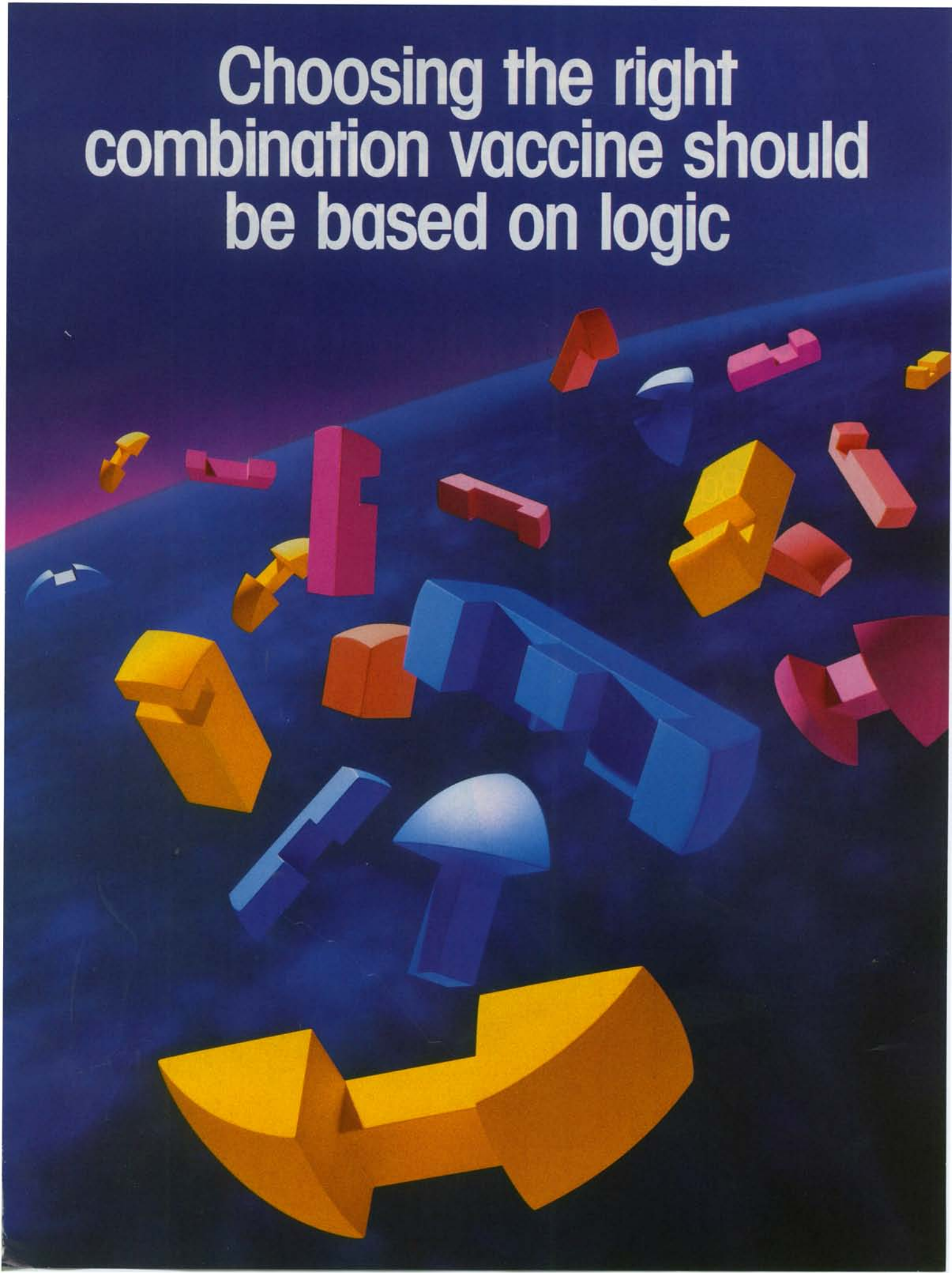
Choosing the right combination vaccine should be based on logic



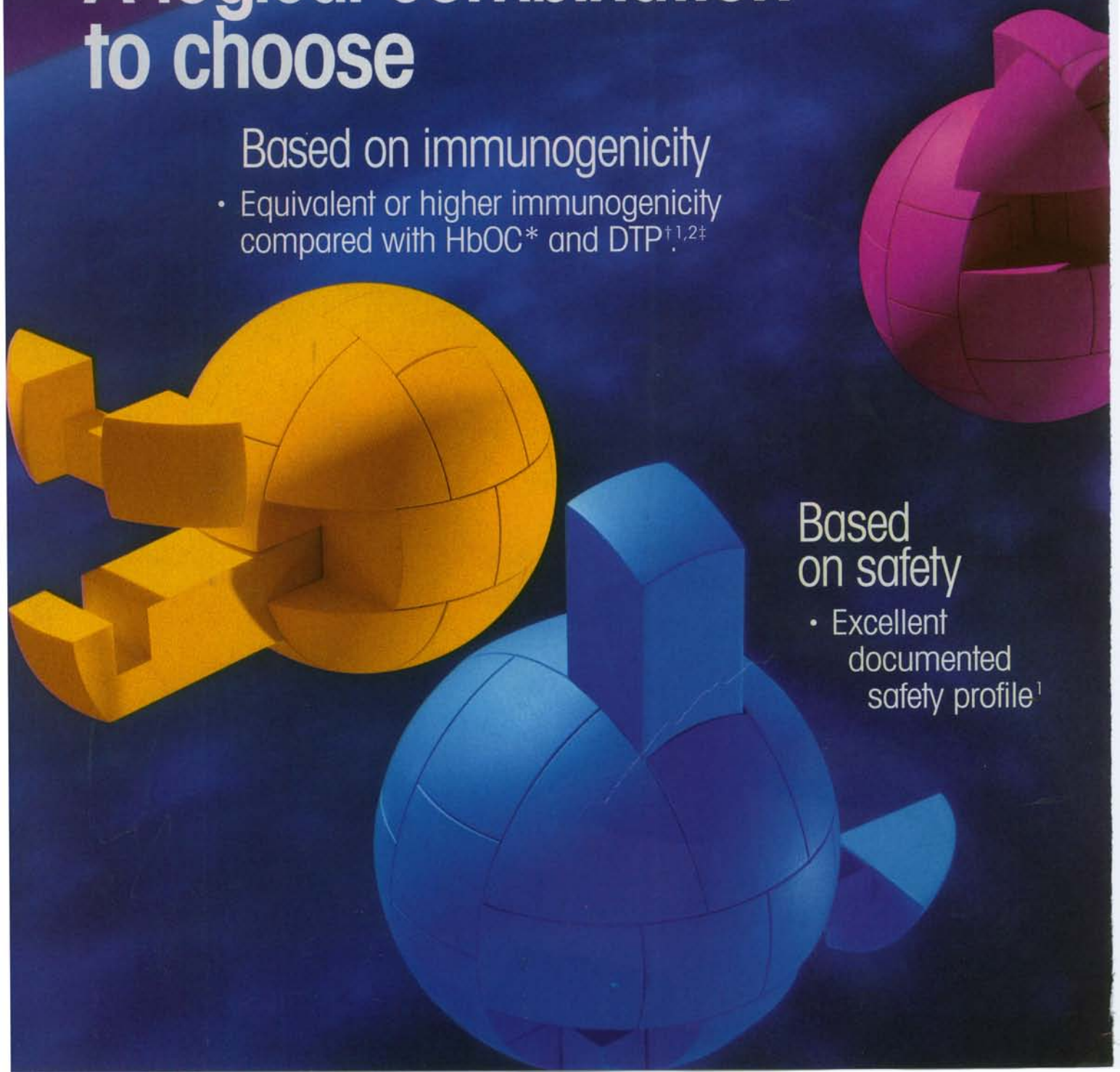
TETRAMUNE™

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

A logical combination to choose

Based on immunogenicity

- Equivalent or higher immunogenicity compared with HbOC* and DTP†.[1,2‡]



Based on safety

- Excellent documented safety profile[1]

Based on convenience

- Ready-to-use, 10-dose vials—*no reconstitution required*

Based on recommended scheduling

- Recommended by the AAP and the ACIP
- A single 0.5 mL injection recommended at 2, 4, 6, and 15 months of age§

*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.

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

§DTaP or DTP should be given at 4 to 6 years of age to complete the recommended 5-dose DTP immunization series.

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). Abstract #1028.

To order, call 1-800-L-E-D-E-R-L-E (533-3753) or contact your local Lederle Medical Representative.

TETRAMUNE™

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

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

Combined vaccine logic

TETRAMUNE™

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

Brief Summary

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

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

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

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

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

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

AN IMMEDIATE ANAPHYLACTIC REACTION.

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

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

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

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

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

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

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

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

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

WARNINGS

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

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

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

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

CONVULSIONS WITH OR WITHOUT FEVER OCCURRING WITHIN 3 DAYS.

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

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

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

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

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

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

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

PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

* within 72 hours of immunization

† within 4 days of immunization

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

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

‖ perceived fever

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

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

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

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

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

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

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

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

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

DOSAGE AND ADMINISTRATION

For Intramuscular Use Only.

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

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

Distributed by
LEDERLE-PRAXIS BIOLOGICALS
A Division of American Cyanamid Company
Wayne, NJ 07470

and

PRAXIS BIOLOGICS, INC.
A Subsidiary of American Cyanamid Company
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REV 3/93
L-32092-93

BECAUSE YOUR MIGRAINE PATIENTS MAY NOT BE TELLING YOU HOW THEY REALLY FEEL ABOUT THEIR CURRENT TREATMENT...

"I don't want to bother
my doctor again ...

I'll just continue with my current treatment."

MORE OF YOUR PATIENTS MAY

Because it works fast.[1]

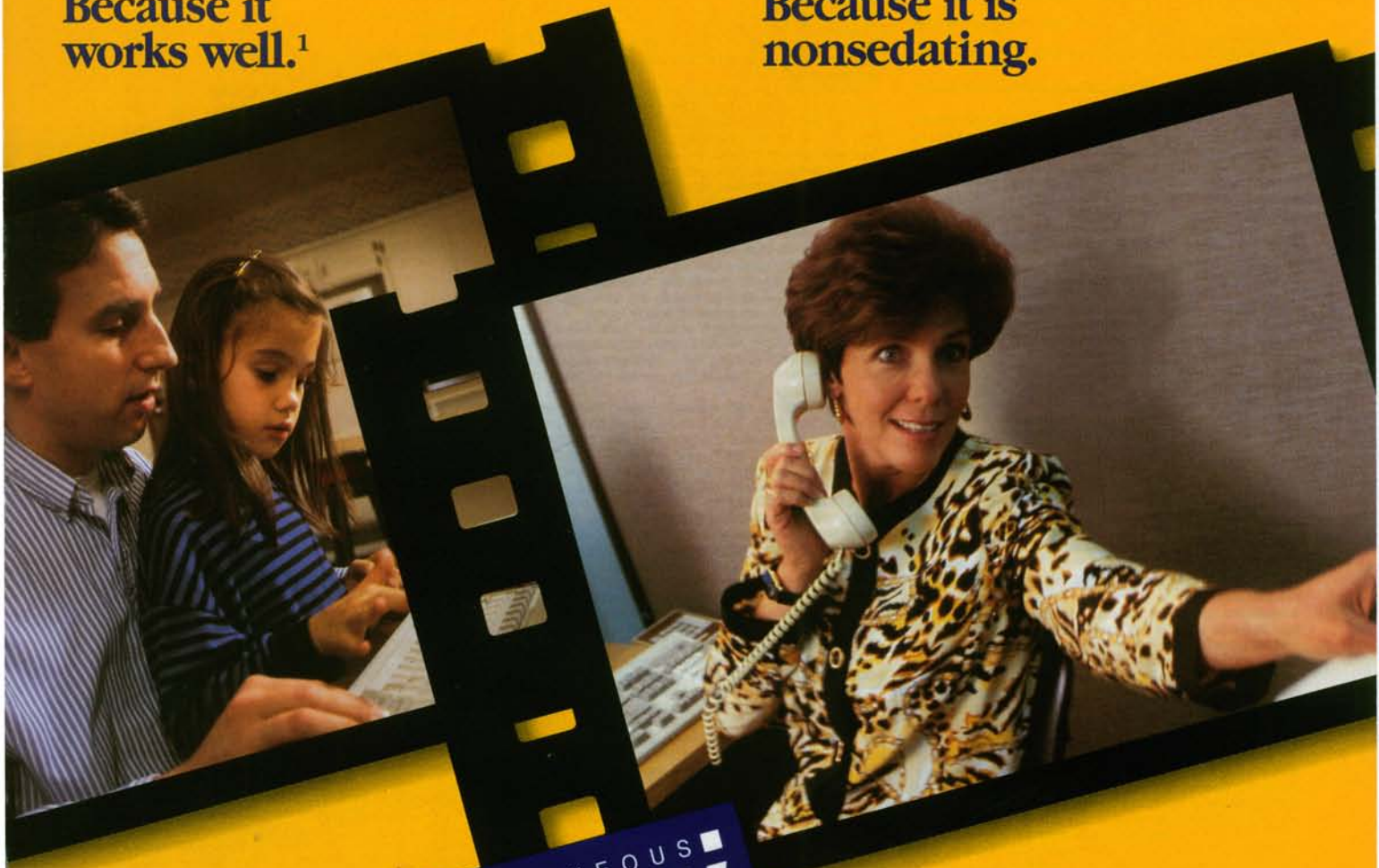
The most frequently reported adverse events associated with IMITREX are injection-site reactions (59%), atypical sensations (e.g., tingling, warm/hot sensation) (42%), and dizziness/vertigo (12%). IMITREX is contraindicated in patients with ischemic heart disease, symptoms or signs consistent with ischemic 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). IMITREX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (Please see Precautions.) IMITREX should not be administered to patients with basilar or hemiplegic migraine.

Reference: 1. Cady RK, Wendt JK, Kirchner JR, Sargent JD, Rothrock JF, Skaggs H Jr. Treatment of acute migraine with subcutaneous sumatriptan. *JAMA*. June 1991;265:2831-2835.

BENEFIT FROM IMITREX

Because it works well.[1]

Because it is nonsedating.



SUBCUTANEOUS

IMITREX®

SUMATRIPTAN SUCCINATE

MIGRAINE RELIEF THAT CAN CHANGE PATIENTS' LIVES

Please consult Brief Summary of Prescribing Information on 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 (ECG) 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; myocardial infarction; and 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.

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.

As with other acute migraine therapies, before treating headaches in patients not previously diagnosed as migraineurs and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions. There have been rare reports where patients received sumatriptan for severe headaches that were subsequently shown to have been secondary to an evolving neurological lesion (cerebrovascular accident, subarachnoid hemorrhage). In this regard, it should be noted that migraineurs may be at increased risk of certain cerebrovascular events (e.g., cerebrovascular accident, transient ischemic attack).

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 text of 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 US, a retrospective analysis of 282 patients who had been using prophylactic drugs (verapamil n=63, amitriptyline n=57, propranolol n=94, for 45 other drugs n=123) were compared to those who had not used prophylaxis (n=452). There were no differences in relief rates at 60 minutes postdose for Imitrex Injection, whether or not prophylactic medications were used. There were also no differences in overall adverse event rates between the two groups.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Cardiovascular: Infrequent were hypertension, hypotension, bradycardia, tachycardia, palpitations, pulsating sensations, various transient ECG 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, cerebrovascular accident, dysphasia, subarachnoid hemorrhage, and arrhythmias (atrial fibrillation, ventricular fibrillation, and ventricular tachycardia). Hypersensitivity to Imitrex Injection has been reported, including anaphylactoid reactions, rash, urticaria, pruritus, erythema, and shortness of breath.

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

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

October 1993 RL-070 SUC8

IMX455RO

Printed in USA

January 1994

Once-A-Day

Adalat® CC
nifedipine EXTENDED RELEASE TABLETS

30mg, 60mg & 90mg

Real Value for Real People with Hypertension

Real Therapeutic Value

- The benefits of long-acting nifedipine therapy for hypertension*[1]

Real Human Value

- Convenient, well-tolerated therapy
- Peripheral edema and headache were the most common dose-related adverse events reported; flushing/heat sensation, dizziness, and fatigue/asthenia were all reported at an incidence of 4%

Real Economic Value

- Lower price (AWP) than Procardia XL® 30 mg, 60 mg and 90 mg—**potential 25% savings**†[2]

*Not indicated for angina. Take on an empty stomach. Careful titration may be necessary when switching between Procardia XL® and Adalat® CC. Procardia XL is a registered trademark of Pfizer Labs Division, Pfizer Inc.

†Calculations based on suggested Average Wholesale Price (AWP).

Please see brief summary of Prescribing Information on back of this page.

"Save as much as $111† a year? I could replace the worn linoleum."

Once-A-Day

Adalat® CC

nifedipine EXTENDED RELEASE TABLETS

30mg, 60mg & 90mg

Start with*

℞

Adalat CC
30mg
once daily

Titrate, if necessary*

℞

Adalat CC
60mg
once daily

*Please see DOSAGE AND ADMINISTRATION section in brief summary of Prescribing Information below.

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION
For Oral Use

PZ100744BS 5/93

INDICATION AND USAGE: ADALAT CC is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

CONTRAINDICATIONS: Known hypersensitivity to nifedipine.

WARNINGS: Excessive Hypotension: Although in most patients the hypotensive effect of nifedipine is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients using concomitant beta-blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients who received immediate release capsules together with a beta-blocking agent and who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of nifedipine and a beta-blocker, but the possibility that it may occur with nifedipine alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In nifedipine-treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for nifedipine to be washed out of the body prior to surgery.

Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those who have severe obstructive coronary artery disease, have developed well documented increased frequency, duration and/or severity of angina or acute myocardial infarction upon starting nifedipine or at the time of dosage increase. The mechanism of this effect is not established.

Beta-Blocker Withdrawal: When discontinuing a beta-blocker it is important to taper its dose, if possible, rather than stopping abruptly before beginning nifedipine. Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of nifedipine treatment will not prevent this occurrence and on occasion has been reported to increase it.

Congestive Heart Failure: Rarely, patients (usually while receiving a beta-blocker) have developed heart failure after beginning nifedipine. Patients with tight aortic stenosis may be at greater risk for such an event, as the unloading effect of nifedipine would be expected to be of less benefit to these patients, owing to their fixed impedance to flow across the aortic valve.

PRECAUTIONS: General - Hypotension: Because nifedipine decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of ADALAT CC is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure (See WARNINGS).

Peripheral Edema: Mild to moderate peripheral edema occurs in a dose-dependent manner with ADALAT CC. The placebo subtracted rate is approximately 8% at 30 mg, 12% at 60 mg and 19% at 90 mg daily. This edema is a localized phenomenon, thought to be associated with vasodilation of dependent arterioles and small blood vessels and not due to left ventricular dysfunction or generalized fluid retention. With patients whose hypertension is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Information for Patients: ADALAT CC is an extended release tablet and should be swallowed whole and taken on an empty stomach. It should not be administered with food. Do not chew, divide or crush tablets.

Laboratory Tests: Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted. The relationship to nifedipine therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms; however, cholestasis with or without jaundice has been reported. A small increase (<5%) in mean alkaline phosphatase was noted in patients treated with ADALAT CC. This was an isolated finding and it rarely resulted in values which fell outside the normal range. Rare instances of allergic hepatitis have been reported with nifedipine treatment. In controlled studies, ADALAT CC did not adversely affect serum uric acid, glucose, cholesterol or potassium.

Nifedipine, like other calcium channel blockers, decreases platelet aggregation *in vitro*. Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some nifedipine patients. This is thought to be a function of inhibition of calcium transport across the platelet membrane. No clinical significance for these findings has been demonstrated.

Positive direct Coombs' test with or without hemolytic anemia has been reported but a causal relationship between nifedipine administration and positivity of this laboratory test, including hemolysis, could not be determined.

Although nifedipine has been used safely in patients with renal dysfunction and has been reported to exert a beneficial effect in certain cases, rare reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to nifedipine therapy is uncertain in most cases but probable in some.

Drug Interactions: Beta-adrenergic blocking agents: (See WARNINGS).

ADALAT CC was well tolerated when administered in combination with a beta blocker in 187 hypertensive patients in a placebo-controlled clinical trial. However, there have been occasional literature reports suggesting that the combination of nifedipine and beta-adrenergic blocking drugs may increase the likelihood of congestive heart failure, severe hypotension, or exacerbation of angina in patients with cardiovascular disease.

Digitalis: Since there have been isolated reports of patients with elevated digoxin levels, and there is a possible interaction between digoxin and ADALAT CC, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing ADALAT CC to avoid possible over- or under-digitalization.

Coumarin Anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom nifedipine was administered. However, the relationship to nifedipine therapy is uncertain.

Quinidine: There have been rare reports of an interaction between quinidine and nifedipine (with a decreased plasma level of quinidine).

Cimetidine: Both the peak plasma level of nifedipine and the AUC may increase in the presence of cimetidine. Ranitidine produces smaller non-significant increases. This effect of cimetidine may be mediated by its known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of nifedipine. If nifedipine therapy is initiated in a patient currently receiving cimetidine, cautious titration is advised.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Nifedipine was administered orally to rats for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative.

Pregnancy: Pregnancy Category C. In rodents, rabbits and monkeys, nifedipine has been shown to have a variety of embryotoxic, placentotoxic and fetotoxic effects, including stunted fetuses (rats, mice and rabbits), digital anomalies (rats and rabbits), rib deformities (mice), cleft palate (mice), small placentas and underdeveloped chorionic villi (monkeys), embryonic and fetal deaths (rats, mice and rabbits), prolonged pregnancy (rats; not evaluated in other species), and decreased neonatal survival (rats; not evaluated in other species). On a mg/kg or mg/m^2 basis, some of the doses associated with these various effects are higher than the maximum recommended human dose and some are lower, but all are within an order of magnitude of it.

The digital anomalies seen in nifedipine-exposed rabbit pups are strikingly similar to those seen in pups exposed to phenytoin, and these are in turn similar to the phalangeal deformities that are the most common malformation seen in human children with *in utero* exposure to phenytoin.

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

Nursing Mothers: Nifedipine is excreted in human milk. Therefore, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE EXPERIENCES: The incidence of adverse events during treatment with ADALAT CC in doses up to 90 mg daily were derived from multi-center placebo-controlled clinical trials in 370 hypertensive patients. Atenolol 50 mg once daily was used concomitantly in 187 of the 370 patients on ADALAT CC and in 64 of the 126 patients on placebo. All adverse events reported during ADALAT CC therapy were tabulated independently of their causal relationship to medication.

The most common adverse event reported with ADALAT® CC was peripheral edema. This was dose related and the frequency was 18% on ADALAT CC 30 mg daily, 22% on ADALAT CC 60 mg daily and 29% on ADALAT CC 90 mg daily versus 10% on placebo.

Other common adverse events reported in the above placebo-controlled trials include: Headache (19%, versus 13% placebo incidence); Flushing/heat sensation (4%, versus 0% placebo incidence); Dizziness (4%, versus 2% placebo incidence); Fatigue/asthenia (4%, versus 4% placebo incidence); Nausea (2%, versus 1% placebo incidence); Constipation (1%, versus 0% placebo incidence).

Where the frequency of adverse events with ADALAT CC and placebo is similar, causal relationship cannot be established.

The following adverse events were reported with an incidence of 3% or less in daily doses up to 90 mg:

Body as a Whole/Systemic: chest pain, leg pain **Central Nervous System:** paresthesia, vertigo **Dermatologic:** rash **Gastrointestinal:** constipation **Musculoskeletal:** leg cramps **Respiratory:** epistaxis, rhinitis **Urogenital:** impotence, urinary frequency

Other adverse events reported with an incidence of less than 1.0% were:

Body as a Whole/Systemic: cellulitis, chills, facial edema, neck pain, pelvic pain, pain **Cardiovascular:** atrial fibrillation, bradycardia, cardiac arrest, extrasystole, hypotension, palpitations, phlebitis, postural hypotension, tachycardia, cutaneous angiectases **Central Nervous System:** anxiety, confusion, decreased libido, depression, hypertonia, insomnia, somnolence **Dermatologic:** pruritus, sweating **Gastrointestinal:** abdominal pain, diarrhea, dry mouth, dyspepsia, esophagitis, flatulence, gastrointestinal hemorrhage, vomiting **Hematologic:** lymphadenopathy **Metabolic:** gout, weight loss **Musculoskeletal:** arthralgia, arthritis, myalgia **Respiratory:** dyspnea, increased cough, rales, pharyngitis **Special Senses:** abnormal vision, amblyopia, conjunctivitis, diplopia, tinnitus **Urogenital/Reproductive:** kidney calculus, nocturia, breast engorgement

The following adverse events have been reported rarely in patients given nifedipine in other formulations: allergenic hepatitis, alopecia, anemia, arthritis with ANA (+), depression, erythromelalgia, exfoliative dermatitis, fever, gingival hyperplasia, gynecomastia, leukopenia, mood changes, muscle cramps, nervousness, paranoid syndrome, purpura, shakiness, sleep disturbances, syncope, taste perversion, thrombocytopenia, transient blindness at the peak plasma level, tremor and urticaria.

DOSAGE AND ADMINISTRATION: Dosage should be adjusted according to each patient's needs. It is recommended that ADALAT CC be administered orally once daily on an empty stomach. ADALAT CC is an extended release dosage form and tablets should be swallowed whole, not bitten or divided. In general, titration should proceed over a 7-14 day period starting with 30 mg once daily. Upward titration should be based on therapeutic efficacy and safety. The usual maintenance dose is 30 mg to 60 mg once daily. Titration to doses above 90 mg daily is not recommended.

If discontinuation of ADALAT CC is necessary, sound clinical practice suggests that the dosage should be decreased gradually with close physician supervision.

Care should be taken when dispensing ADALAT CC to assure that the extended release dosage form has been prescribed.

PZ100744BS 5/93 3060
Printed in USA

Real People, Real Needs, Real Value

References:

1. Data on file, Miles Inc.
2. *Redbook Update.* Montvale, NJ, Medical Economics Data, Inc., October 1993;p. 34.

MILES

Pharmaceutical Division

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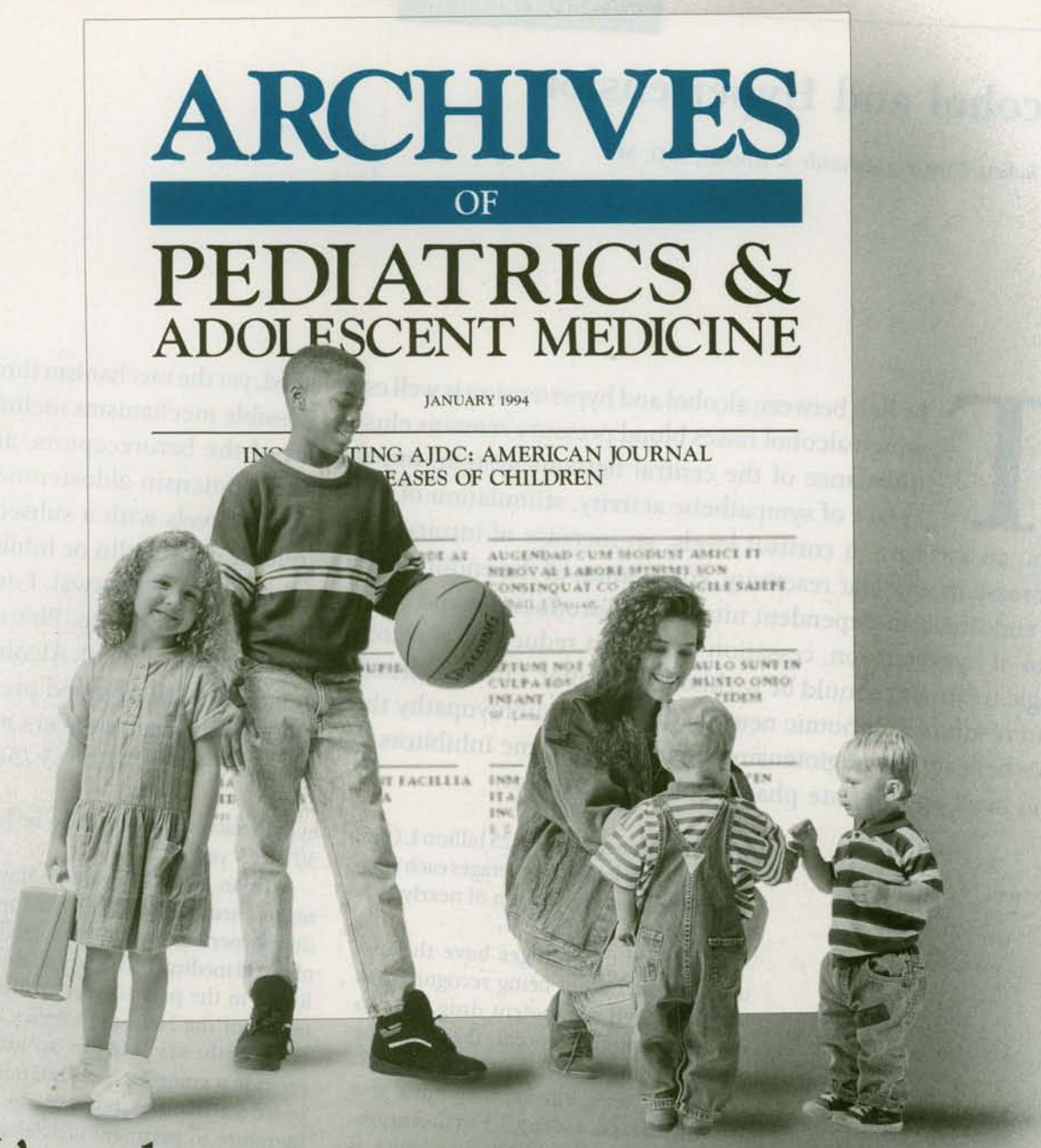

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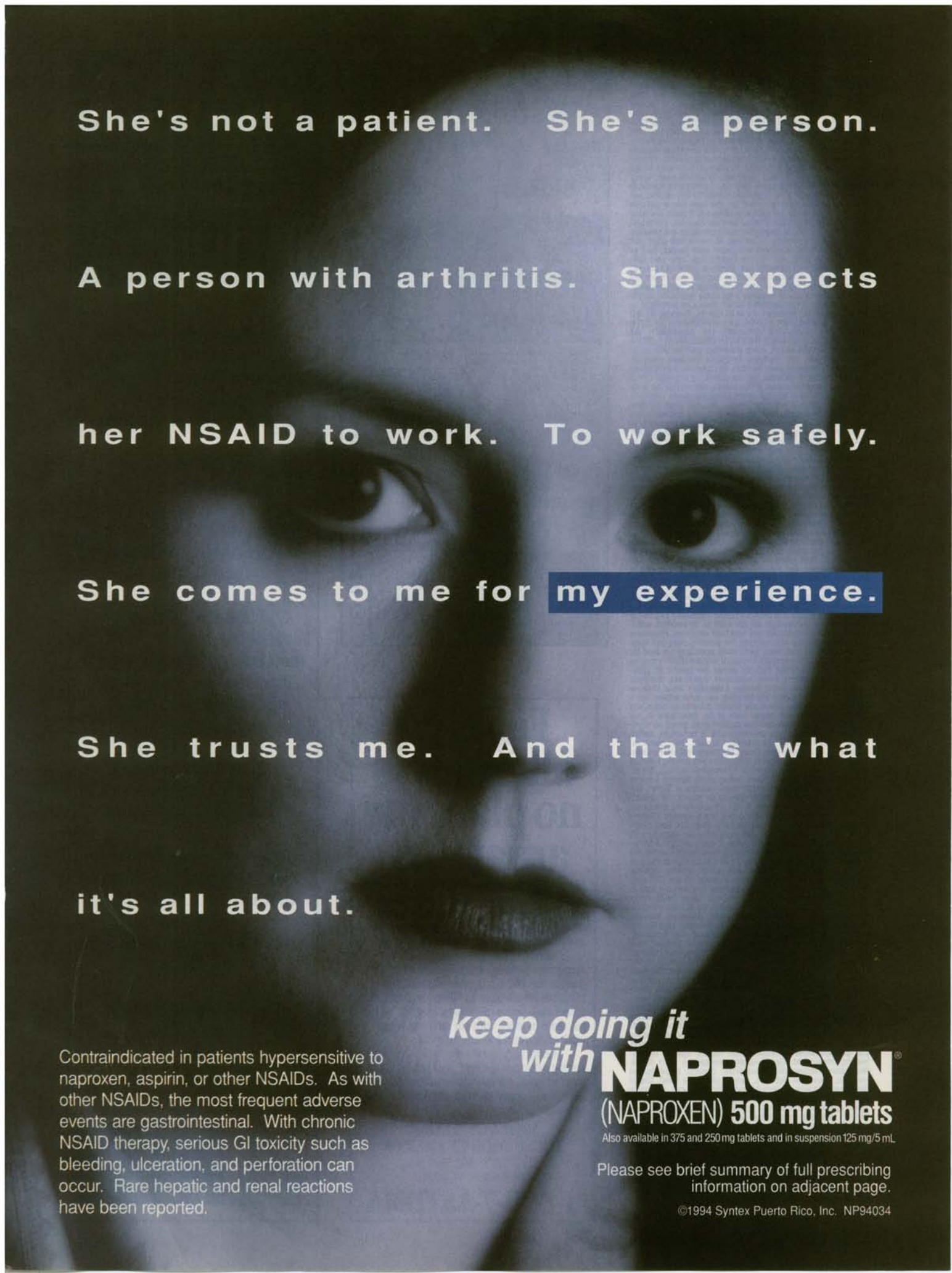
She's not a patient. She's a person.
A person with arthritis. She expects
her NSAID to work. To work safely.
She comes to me for my experience.
She trusts me. And that's what
it's all about.
keep doing it
with NAPROSYN®
(NAPROXEN) 500 mg tablets
Also available in 375 and 250 mg tablets and in suspension 125 mg/5 mL
Contraindicated in patients hypersensitive to naproxen, aspirin, or other NSAIDs. As with other NSAIDs, the most frequent adverse events are gastrointestinal. With chronic NSAID therapy, serious GI toxicity such as bleeding, ulceration, and perforation can occur. Rare hepatic and renal reactions have been reported.
Please see brief summary of full prescribing information on adjacent page.
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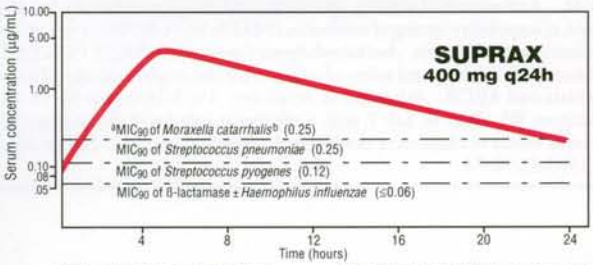
Working Continuously 24 Hours a Day... Once a Day

SUPRAX maintains inhibitory concentrations above MIC_{90} for virtually 24 hours[1]*



[a] MIC_{90} values from Jones and Barry.[2] [b] 17 of 20 strains were ß-lactamase producing.

Proven Clinical Efficacy

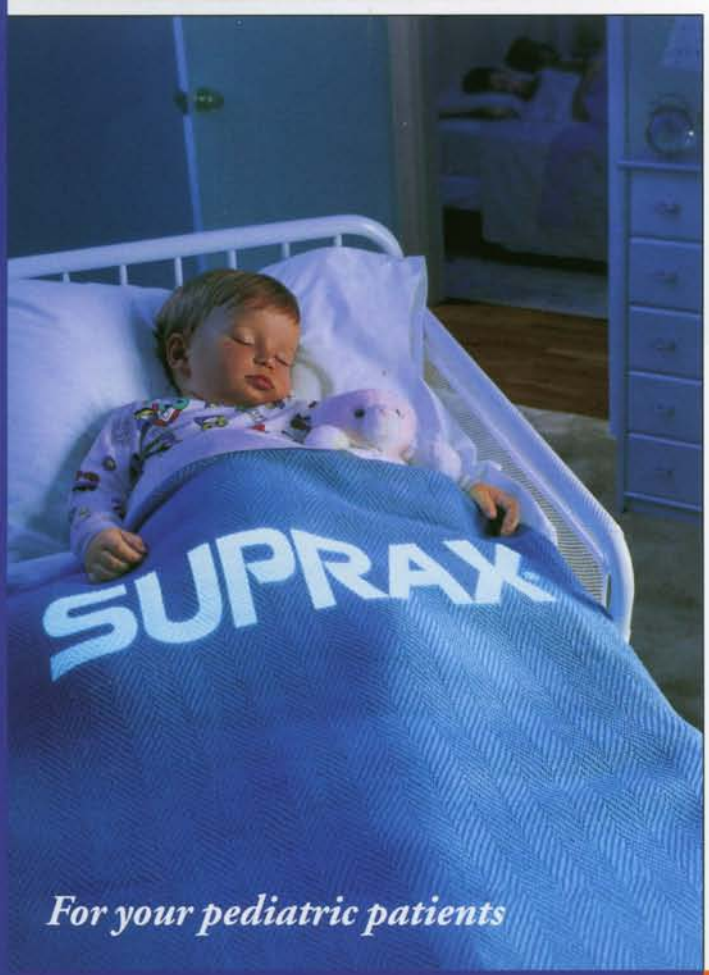
In Bronchitis[3†]
Cured: 67%
Improved: 29%
96% (n=8,993)

In Pharyngitis/Tonsillitis[1†]
Cured: 89%
Improved: 10%
99% (n=300)

In Otitis Media[4†]
97% cured/improved (n=29)

*Although a useful guide, *in vitro* activity does not necessarily correlate with clinical response.

†Due to indicated susceptible organisms.



ONCE-A-DAY

SUPRAX®

cefixime

TABLETS 400 mg
ORAL SUSPENSION 100 mg / 5 mL

Working 24 hours a day

Please see brief summary of Prescribing Information on adjacent page for WARNINGS, ADVERSE REACTIONS, and CONTRAINDICATIONS. GI side effects are the most frequently reported adverse effects.

SUPRAX is administered as a single dose, once a day, or if preferred, in equally divided doses twice a day.

ONCE-A-DAY SUPRAX®

cefixime

TABLETS
400 mg
ORAL SUSPENSION
100 mg/5 mL

Working 24 hours a day

References: 1. Data on file. Lederle Laboratories, Pearl River, NY. **2.** Jones RN, Barry AL. Antimicrobial activity, spectrum, and recommendations for disk diffusion susceptibility testing of ceftibuten (7432-S; SCH 39720), a new orally administered cephalosporin. *Antimicrob Agents Chemother.* 1988;32:1576-1582. **3.** Stratton CW. Efficacy and safety of cefixime for the empiric therapy of acute bronchitis and AECB. *Infections in Medicine.* 1993;10(suppl B):11-15. **4.** Rodriguez WJ, Khan W, Sait T, et al. Cefixime *vs.* cefaclor in the treatment of acute otitis media in children: a randomized, comparative study. *Pediatr Infect Dis J.* 1993;12:70-74.

Brief Summary

SUPRAX®
Cefixime
Oral

Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE

SUPRAX is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Uncomplicated Urinary Tract Infections caused by *Escherichia coli* and *Proteus mirabilis*.

Otitis Media caused by *Haemophilus influenzae* (beta-lactamase positive and negative strains), *Moraxella (Branhamella) catarrhalis*, (most of which are beta-lactamase positive), and *Streptococcus pyogenes*.*

Note: For information on otitis media caused by *Streptococcus pneumoniae*, see **CLINICAL STUDIES** section.

Pharyngitis and Tonsillitis, caused by *S pyogenes*.

Note: Penicillin is the usual drug of choice in the treatment of *S pyogenes* infections, including the prophylaxis of rheumatic fever. SUPRAX is generally effective in the eradication of *S pyogenes* from the nasopharynx; however, data establishing the efficacy of SUPRAX in the subsequent prevention of rheumatic fever are not available.

Acute Bronchitis and Acute Exacerbations of Chronic Bronchitis, caused by *S pneumoniae* and *H influenzae* (beta-lactamase positive and negative strains).

Uncomplicated Gonorrhea (Cervical/Urethral), caused by *Neisseria gonorrhoeae* (penicillinase- and nonpenicillinase-producing strains).

Appropriate cultures and susceptibility studies should be performed to determine the causative organism and its susceptibility to SUPRAX; however, therapy may be started while awaiting the results of these studies. Therapy should be adjusted, if necessary, once these results are known.

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

CLINICAL STUDIES

In clinical trials of otitis media in nearly 400 children between the ages of 6 months to 10 years, *S pneumoniae* was isolated from 47% of the patients, *H influenzae* from 34%, *M (B) catarrhalis* from 15%, and *S pyogenes* from 4%.

The overall response rate of *S pneumoniae* to cefixime was approximately 10% lower and that of *H influenzae* or *M (B) catarrhalis* approximately 7% higher (12% when beta-lactamase positive strains of *H influenzae* are included) than the response rates of these organisms to the active control drugs.

In these studies, patients were randomized and treated with either cefixime at dose regimens of 4 mg/kg BID or 8 mg/kg QD, or with a standard antibiotic regimen. Sixty-nine percent to 70% of the patients in each group had resolution of signs and symptoms of otitis media when evaluated 2 to 4 weeks posttreatment, but persistent effusion was found in 15% of the patients. When evaluated at the completion of therapy, 17% of patients receiving cefixime and 14% of patients receiving effective comparative drugs (18% including those patients who had *H influenzae* resistant to the control drug and who received the control antibiotic) were considered to be treatment failures. By the 2- to 4-week follow-up, a total of 30% to 31% of patients had evidence of either treatment failure or recurrent disease.

Bacteriological Outcome of Otitis Media at 2 to 4 Weeks Posttherapy
Based on Repeat Middle Ear Fluid Culture or
Extrapolation from Clinical Outcome

Organism	Cefixime[a] 4 mg/kg BID	Cefixime[a] 8 mg/kg QD	Control[a] drugs
Streptococcus pneumoniae	48/70 (69%)	18/22 (82%)	82/100 (82%)
Haemophilus influenzae beta-lactamase negative	24/34 (71%)	13/17 (76%)	23/34 (68%)
Haemophilus influenzae beta-lactamase positive	17/22 (77%)	9/12 (75%)	1/1[b]
Moraxella (Branhamella) catarrhalis	26/31 (84%)	5/5	18/24 (75%)
S pyogenes	5/5	3/3	6/7
All Isolates	120/162 (74%)	48/59 (81%)	130/166 (78%)

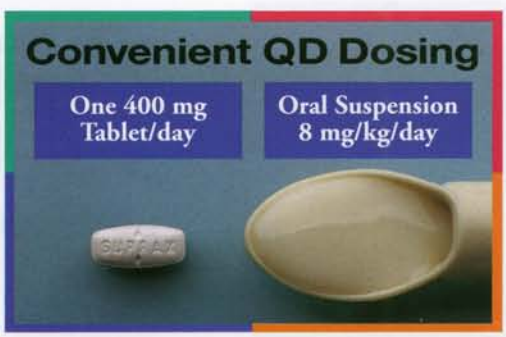
[a] Number eradicated/number isolated.

[b] An additional 20 beta-lactamase positive strains of *H influenzae* were isolated, but were excluded from this analysis because they were resistant to the control antibiotic. In 19 of these, the clinical course could be assessed, and a favorable outcome occurred in 10. When these cases are included in the overall bacteriological evaluation of therapy with the control drugs, 140/185 (76%) of pathogens were considered to be eradicated.

Tablets should not be substituted for suspension when treating otitis media.

CONTRAINDICATIONS

SUPRAX is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.



SUPRAX® cefixime

WARNINGS

BEFORE THERAPY WITH SUPRAX IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO SUPRAX OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Administer cautiously to allergic patients.

Treatment with broad-spectrum antibiotics, including SUPRAX, alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of severe antibiotic-associated diarrhea including pseudomembranous colitis.

Pseudomembranous colitis has been reported with the use of SUPRAX and other broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider this diagnosis in patients who develop diarrhea in association with the use of antibiotics. Symptoms of pseudomembranous colitis may occur during or after antibiotic treatment and may range in severity from mild to life-threatening. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, management should include fluids, electrolytes, and protein supplementation. If the colitis does not improve after the drug has been discontinued, or if the symptoms are severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes of colitis should be excluded.

PRECAUTIONS

General: Use, especially when prolonged, may result in overgrowth of resistant organisms. If superinfection occurs during therapy, take appropriate measures.

Carefully monitor patients on dialysis. Adjust dosage of SUPRAX in patients with renal impairment and those undergoing continuous ambulatory peritoneal dialysis and hemodialysis. (See **DOSAGE AND ADMINISTRATION** in package insert.)

Prescribe cautiously in patients with a history of gastrointestinal disease, particularly colitis.

Drug Interactions: No significant drug interactions have been reported to date.

Drug/Laboratory Test Interactions: A false-positive reaction for ketones in the urine may occur with tests using nitroprusside but not with those using nitroferricyanide.

SUPRAX administration may result in a false-positive reaction for glucose in the urine using Clinitest®,** Benedict's solution, or Fehling's solution. Use glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix®** or Tes-Tape®**).

A false-positive direct Coombs test has been reported during treatment with other cephalosporin antibiotics; therefore, it should be recognized that a positive Coombs test may be due to the drug.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although no lifetime animal studies have been conducted to evaluate carcinogenic potential, no mutagenic potential of SUPRAX was found in standard laboratory tests. In rats, reproductive studies revealed no fertility impairment at doses up to 125 times the adult therapeutic dose.

Usage in Pregnancy: *Pregnancy Category B:* Reproduction studies have been performed in mice and rats at doses up to 400 times the human dose and have revealed no evidence of harm to the fetus due to SUPRAX. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: SUPRAX has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

Nursing Mothers: It is not known whether SUPRAX is excreted in human milk. Consider discontinuing nursing temporarily during treatment with this drug.

Pediatric Use: Safety and effectiveness of SUPRAX in children aged less than 6 months have not been established.

The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension was comparable to that seen in adult patients receiving tablets.

ADVERSE REACTIONS

Most adverse reactions observed in clinical trials were of a mild and transient nature. Five percent (5%) of patients in the US trials discontinued therapy because of drug-related adverse reactions. The most commonly seen adverse reactions in US trials of the tablet formulation were gastrointestinal events, which were reported in 30% of adult patients on either the BID or the QD regimen. Clinically mild gastrointestinal side effects occurred in 20% of all patients, moderate events occurred in 9% of all patients, and severe adverse reactions occurred in 2% of all patients. Individual event rates included diarrhea 16%, loose or frequent stools 6%, abdominal pain 3%, nausea 7%, dyspepsia 3%, and flatulence 4%. The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension was comparable to that seen in adult patients receiving tablets.

These symptoms usually responded to symptomatic therapy or ceased when SUPRAX was discontinued.

Several patients developed severe diarrhea and/or documented pseudomembranous colitis, and a few required hospitalization.

The following adverse reactions have been reported following the use of SUPRAX. Incidence rates were less than 1 in 50 (less than 2%), except as noted above for gastrointestinal events.

Gastrointestinal: Diarrhea, loose stools, abdominal pain, dyspepsia, nausea, and vomiting. Several cases of documented pseudomembranous colitis were identified during the studies. The onset of pseudomembranous colitis symptoms may occur during or after therapy.

Hypersensitivity Reactions: Skin rashes, urticaria, drug fever, and pruritus. Erythema multiforme, Stevens-Johnson syndrome, and serum sickness-like reactions have been reported.

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

Renal: Transient elevations in BUN or creatinine.

Central Nervous System: Headaches or dizziness.

Hemic and Lymphatic Systems: Transient thrombocytopenia, leukopenia, and eosinophilia. Prolongation in prothrombin time was seen rarely.

Other: Genital pruritus, vaginitis, candidiasis.

The following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Adverse Reactions: Allergic reactions including anaphylaxis, toxic epidermal necrolysis, superinfection, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, and colitis.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see **DOSAGE AND ADMINISTRATION** and **OVERDOSAGE**). If seizures associated with drug therapy occur, discontinue drug. Administer anticonvulsant therapy if clinically indicated.

Abnormal Laboratory Tests: Positive direct Coombs test, elevated bilirubin, elevated LDH, pancytopenia, neutropenia, agranulocytosis.

OVERDOSAGE

Gastric lavage may be indicated; otherwise, no specific antidote exists. Cefixime is not removed in significant quantities from the circulation by hemodialysis or peritoneal dialysis. Adverse reactions in small numbers of healthy adult volunteers receiving single doses up to 2 g of SUPRAX did not differ from the profile seen in patients treated at the recommended doses.

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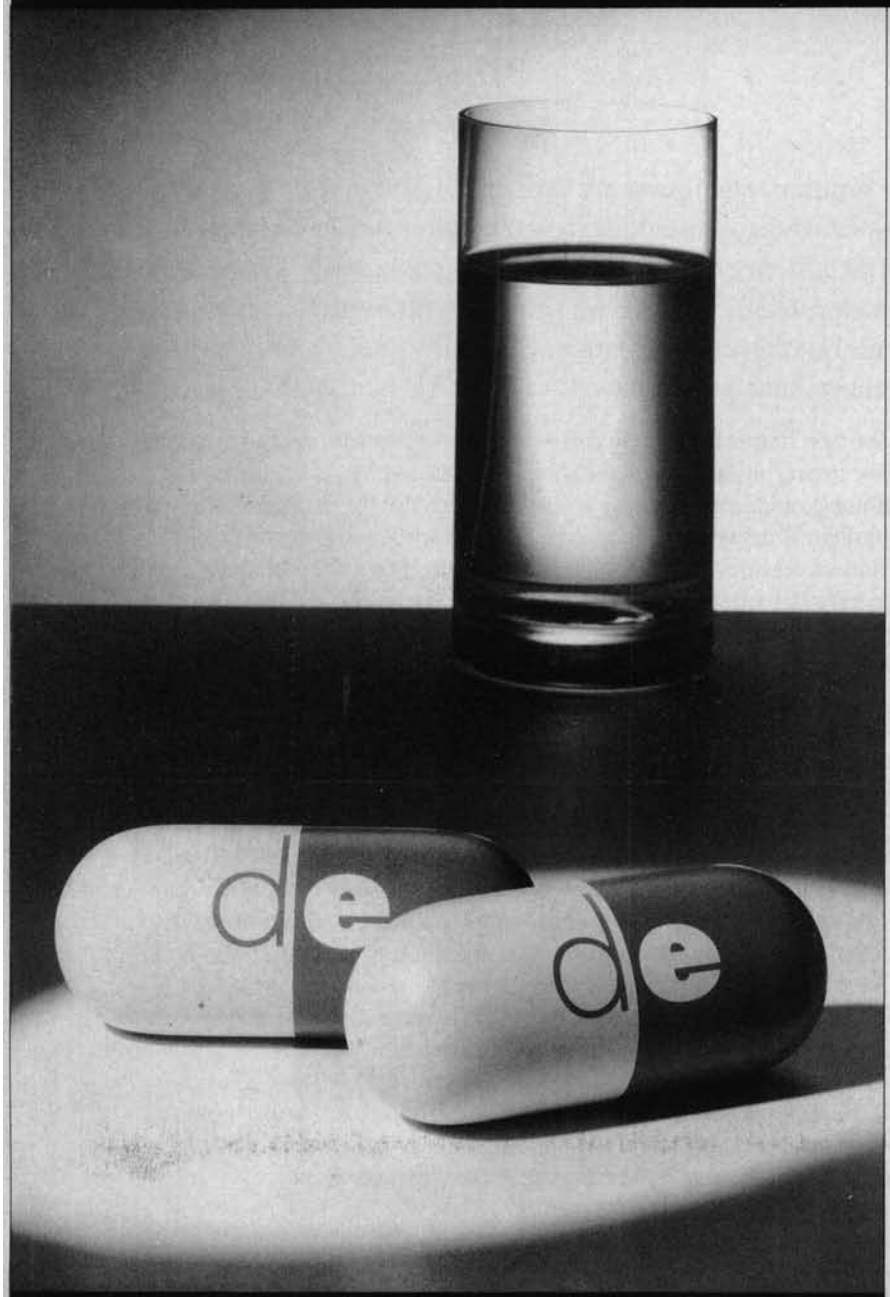

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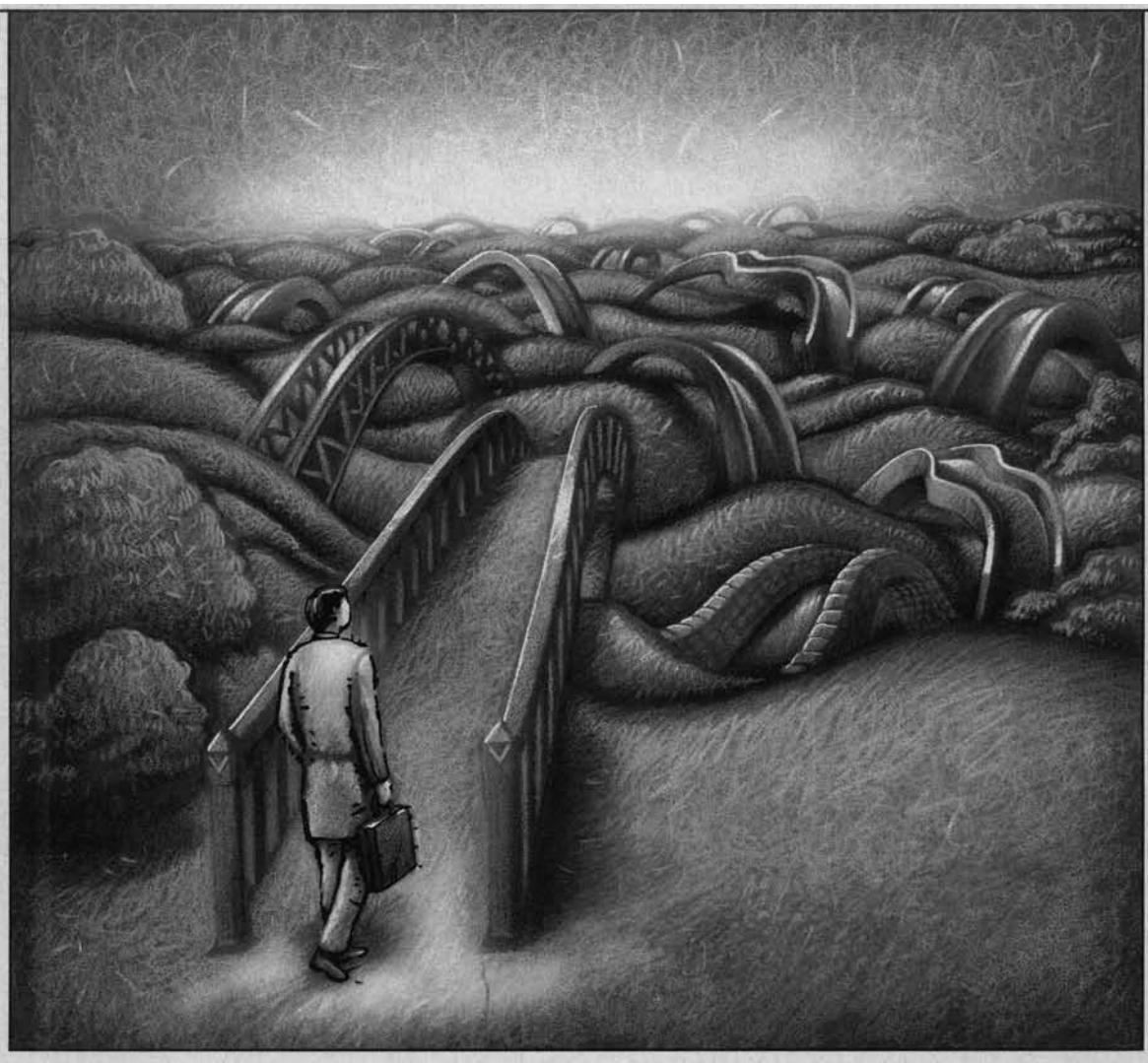

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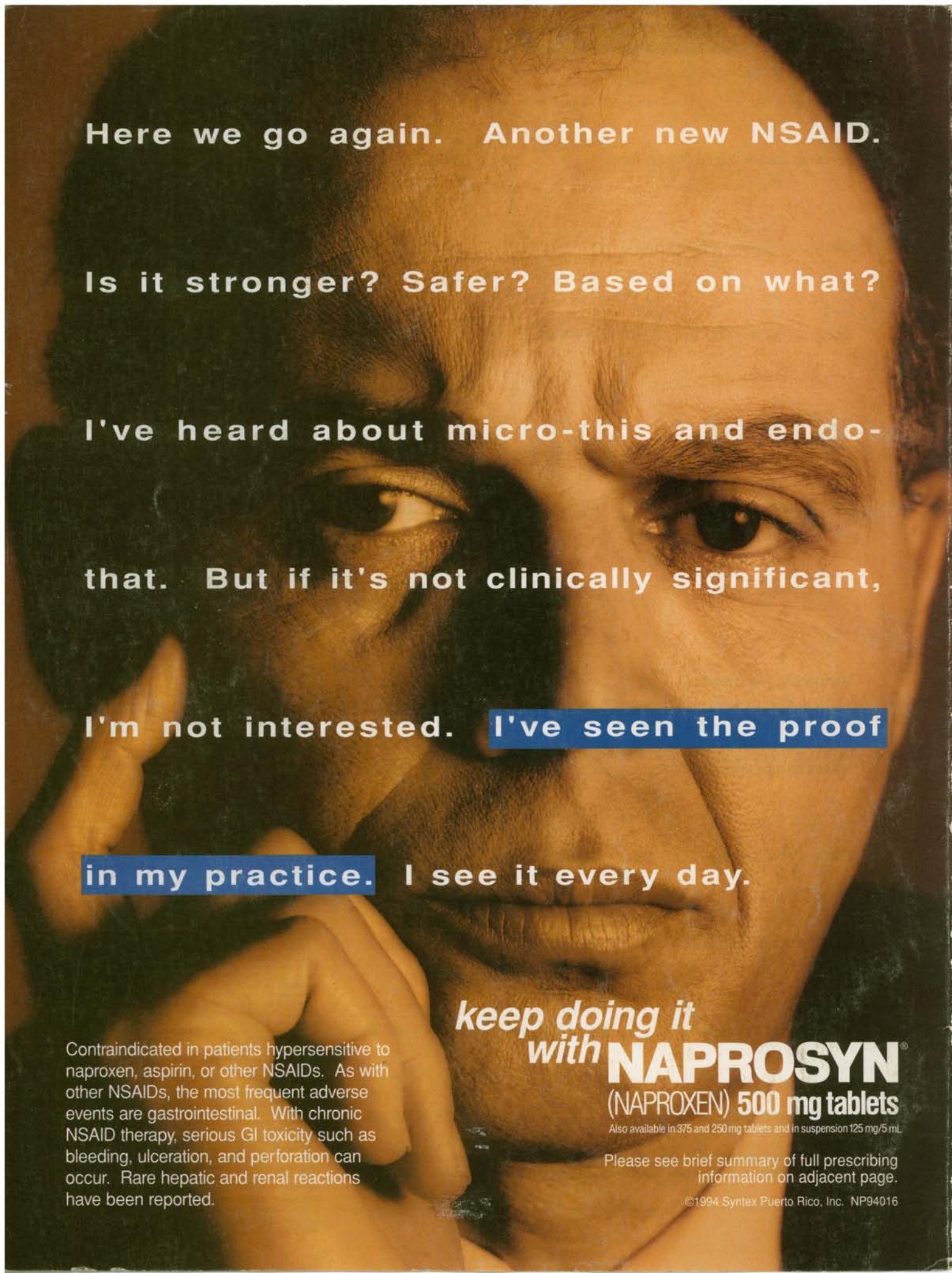
Here we go again. Another new NSAID.
Is it stronger? Safer? Based on what?
I've heard about micro-this and endo-
that. But if it's not clinically significant,
I'm not interested. I've seen the proof
in my practice. I see it every day.
keep doing it
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Contraindicated in patients hypersensitive to naproxen, aspirin, or other NSAIDs. As with other NSAIDs, the most frequent adverse events are gastrointestinal. With chronic NSAID therapy, serious GI toxicity such as bleeding, ulceration, and perforation can occur. Rare hepatic and renal reactions have been reported.