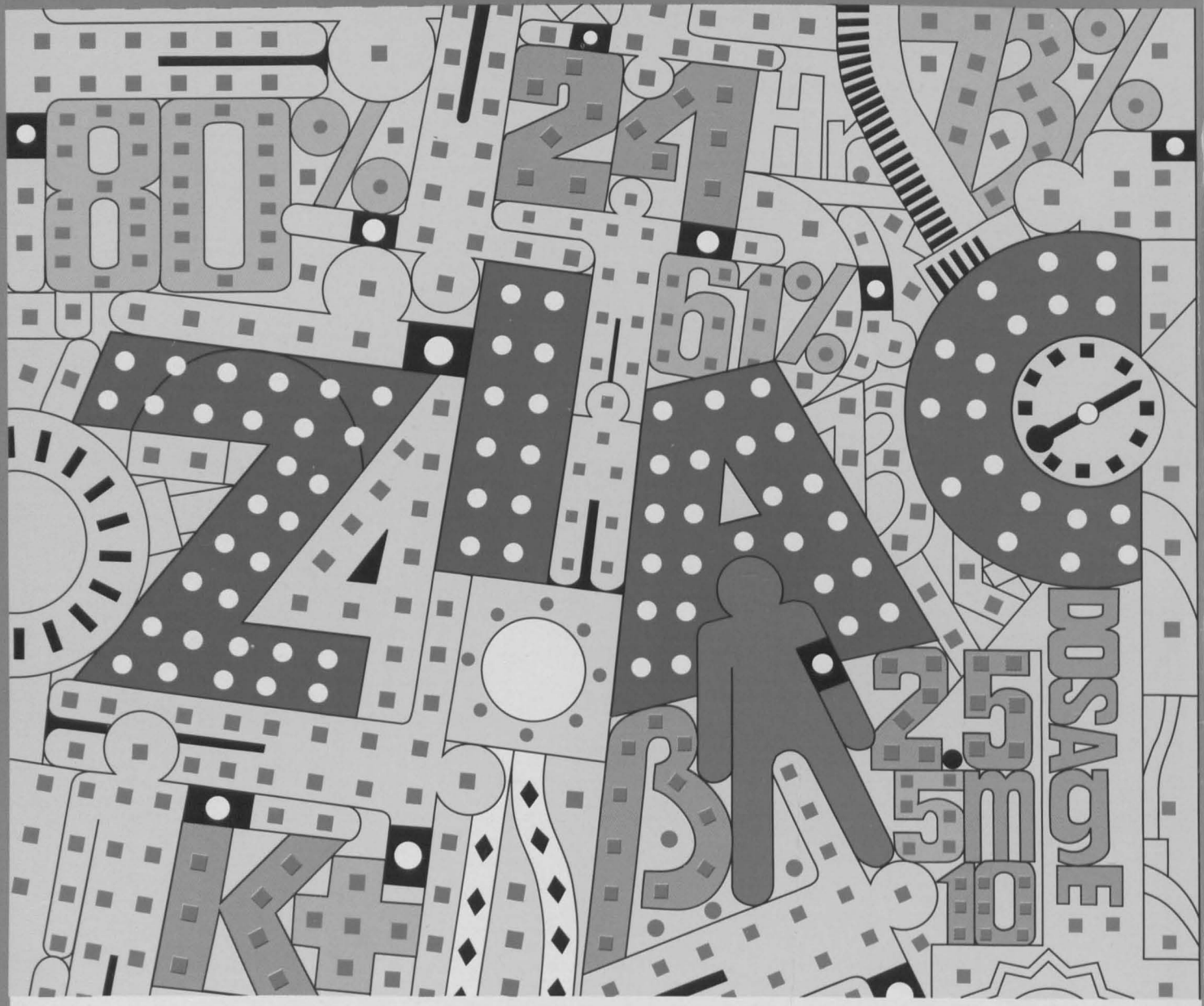
For first-line therapy in mild-to-moderate hypertension

Discover the classic benefits of a beta-blocker and a diuretic...now at low doses for a side-effect profile comparable to placebo[1]*



ZIAC controls mild-to-moderate hypertension in up to 80% of patients[1†]

ZIAC controls blood pressure for a full 24 hours for true once-a-day dosing[2]

ZIAC minimizes traditional beta-blocker- and HCTZ-associated metabolic effects (hypokalemia, hyperuricemia, hypercholesterolemia, hyperglycemia)[1]

*The two most common side effects — dizziness and fatigue — occurred at rates comparable to placebo.

†Clinical trial response rates were: 2.5 mg—61%; 5 mg—73%; 10 mg—80%.

ZIAC is contraindicated in patients in cardiogenic shock, overt cardiac failure (see WARNINGS section of full Prescribing Information), second- or third-degree AV block, marked sinus bradycardia, anuria, and hypersensitivity to either component of this product or to other sulfonamide-derived drugs.

Please see Brief Summary of Prescribing Information on adjacent page.

First-line therapy option

NEW ZIAC™

(bisoprolol fumarate-hydrochlorothiazide)

2.5, 5, & 10 mg Tablets with 6.25 mg HCTZ

First-line therapy option

NEW **ZIAC**™

(bisoprolol fumarate-hydrochlorothiazide)

2.5, 5, & 10 mg Tablets with 6.25 mg HCTZ

References:

1. DeQuattro V, Weir MR. Bisoprolol fumarate/hydrochlorothiazide 6.25 mg: a new, low-dose option for first-line antihypertensive therapy. *Adv Ther.* 1993;10:197-206.
2. Lewin AJ, Lueg MC, Targum S, et al. A clinical trial evaluating the 24-hour effects of bisoprolol/hydrochlorothiazide 5 mg/6.25 mg combination in patients with mild to moderate hypertension. *Clin Cardiol.* 1993;16:732-736.

Brief Summary

ZIAC™ (Bisoprolol Fumarate and Hydrochlorothiazide) Tablets

FOR FULL PRESCRIBING INFORMATION, PLEASE CONSULT PACKAGE INSERT.

DESCRIPTION

ZIAC (bisoprolol fumarate and hydrochlorothiazide) is indicated for the treatment of hypertension. It combines two antihypertensive agents in a once-daily dosage: a synthetic beta$_1$-selective (cardioselective) adrenoceptor blocking agent (bisoprolol fumarate) and a benzothiadiazine diuretic (hydrochlorothiazide).

CLINICAL PHARMACOLOGY

At doses ≥ 20 mg bisoprolol fumarate inhibits beta$_1$-adrenoreceptors located in bronchial and vascular musculature. To retain relative selectivity, it is important to use the lowest effective dose.

CONTRAINDICATIONS

Cardiogenic shock, overt cardiac failure (see **WARNINGS**), second or third degree AV block, marked sinus bradycardia, anuria, and hypersensitivity to either component of this product or to other sulfonamide-derived drugs.

WARNINGS

Cardiac Failure: Beta-blocking agents should be avoided in patients with overt congestive failure.
Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blockers can precipitate cardiac failure. At the first signs or symptoms of heart failure, discontinuation of ZIAC should be considered.
Abrupt Cessation of Therapy: Abrupt cessation of beta-blockers should be avoided. Even in patients without overt coronary artery disease, it may be advisable to taper therapy with ZIAC over approximately 1 week with the patient under careful observation. If withdrawal symptoms occur, beta-blocking agent therapy should be reinstituted, at least temporarily.
Peripheral Vascular Disease: Beta-blockers should be used with caution in patients with peripheral vascular disease.
Bronchospastic Disease: PATIENTS WITH BRONCHOSPASTIC PULMONARY DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS.
Anesthesia and Major Surgery: If used perioperatively, particular care should be taken when anesthetic agents that depress myocardial function, such as ether, cyclopropane, and trichloroethylene, are used.
Diabetes and Hypoglycemia: Beta-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents, should be cautioned. Also, latent diabetes mellitus may become manifest and diabetic patients given thiazides may require adjustment of their insulin dose.
Thyrotoxicosis: Beta-adrenergic blockade may mask clinical signs of hyperthyroidism. Abrupt withdrawal of beta-blockade may be followed by an exacerbation of the symptoms of hyperthyroidism or may precipitate thyroid storm.
Renal Disease: Cumulative effects of the thiazides may develop in patients with impaired renal function. In such patients, thiazides may precipitate azotemia. In subjects with creatinine clearance less than 40 mL/min, the plasma half-life of bisoprolol fumarate is increased up to threefold, as compared to healthy subjects.
Hepatic Disease: ZIAC should be used with caution in patients with impaired hepatic function or progressive liver disease.

PRECAUTIONS

General: *Electrolyte and Fluid Balance Status:* Periodic determination of serum electrolytes should be performed, and patients should be observed for signs of fluid or electrolyte disturbances. Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia. Hypokalemia may develop. Hypokalemia and hypomagnesemia can provoke ventricular arrhythmias or sensitize or exaggerate the response of the heart to the toxic effects of digitalis. Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than salt administration, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice. *Parathyroid Disease:* Calcium excretion is decreased by thiazides, and pathologic changes in the parathyroid glands, with hypercalcemia and hypophosphatemia, have been observed in a few patients on prolonged thiazide therapy. *Hyperuricemia:* Hyperuricemia or acute gout may be precipitated in certain patients receiving thiazide diuretics. Bisoprolol fumarate, alone or in combination with HCTZ, has been associated with increases in uric acid.
Drug Interactions: ZIAC may potentiate the action of other antihypertensive agents used concomitantly. ZIAC should not be combined with other beta-blocking agents. In patients receiving concurrent therapy with clonidine, if therapy is to be discontinued, it is suggested that ZIAC be discontinued for several days before the withdrawal of clonidine.

ZIAC should be used with caution when myocardial depressants or inhibitors of AV conduction or antiarrhythmic agents are used concurrently.

Bisoprolol Fumarate: Concurrent use of rifampin increases the metabolic clearance of bisoprolol fumarate, shortening its elimination half-life. Pharmacokinetic studies document no clinically relevant interactions with other agents given concomitantly, including thiazide diuretics, digoxin and cimetidine. There was no effect of bisoprolol fumarate on prothrombin times in patients on stable doses of warfarin.

While taking beta-blockers, patients with a history of severe anaphylactic reaction may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic and may be unresponsive to the usual doses of epinephrine used to treat allergic reactions.

Hydrochlorothiazide: The following drugs may interact with thiazide diuretics. Alcohol, barbiturates, or narcotics–potentiation of orthostatic hypotension may occur. Dosage adjustment of the antidiabetic drugs (oral agents and insulin) may be required. Other antihypertensive drugs–additive effect or potentiation. Cholestyramine and colestipol resins–single doses of cholestyramine and colestipol resins bind the hydrochlorothiazide and reduce its absorption in the gastrointestinal tract by up to 85 and 43 percent, respectively. Corticosteroids, ACTH–intensified electrolyte depletion, particularly hypokalemia. Possible decreased response to pressor amines but not sufficient to preclude their use. Possible increased responsiveness to muscle relaxants, nondepolarizing. Generally, lithium should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. The administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics.

In patients receiving thiazides, sensitivity reactions may occur with or without a history of allergy or bronchial asthma. Photosensitivity reactions and possible exacerbation or activation of systemic lupus erythematosus have been reported in patients receiving thiazides. The antihypertensive effects of thiazides may be enhanced in the post-sympathectomy patient.
Laboratory Test Interactions: Based on reports involving thiazides, ZIAC may decrease serum levels of protein-bound iodine without signs of thyroid disturbance. Because it includes a thiazide, ZIAC should be discontinued before carrying out tests for parathyroid function (see **PRECAUTIONS**–*Parathyroid Disease*).

ADVERSE REACTIONS

ZIAC: Bisoprolol fumarate/H6.25 mg is well tolerated in most patients. Most adverse effects (AEs) have been mild and transient. In more than 65,000 patients treated worldwide with bisoprolol fumarate, occurrences of bronchospasm have been rare. Discontinuation rates for AEs were similar for B/H6.25 mg and placebo-treated patients.

In the United States, 252 patients received bisoprolol fumarate (2.5, 5, 10, or 40 mg)/H6.25 mg and 144 patients received placebo in two controlled trials. In Study 1, bisoprolol fumarate 5/H6.25 mg was administered for 4 weeks. In Study 2, bisoprolol fumarate 2.5, 10 or 40/H6.25 mg was administered for 12 weeks. All adverse experiences, whether drug-related or not, and drug-related adverse experiences in patients treated with B2.5-10/H6.25 mg, reported during comparable, 4 week treatment periods by at least 2% of bisoprolol fumarate/H6.25 mg-treated patients (plus additional selected adverse experiences) are presented in the following table:

ZIAC™ (Bisoprolol Fumarate and Hydrochlorothiazide) Tablets

Body System/ Adverse Experience	% of Patients with Adverse Experiences*			
	All Adverse Experiences		Drug-related Adverse Experiences	
	Placebo† (n = 144) %	B2.5-40/H6.25† (n = 252) %	Placebo† (n = 144) %	B2.5-10/H6.25† (n = 221) %
Cardiovascular				
bradycardia	0.7	1.1	0.7	0.9
arrhythmia	1.4	0.4	0.0	0.0
peripheral ischemia	0.9	0.7	0.9	0.4
chest pain	0.7	1.8	0.7	0.9
Respiratory				
bronchospasm	0.0	0.0	0.0	0.0
cough	1.0	2.2	0.7	1.5
rhinitis	2.0	0.7	0.7	0.9
URI	2.3	2.1	0.0	0.0
Body as a Whole				
asthenia	0.0	0.0	0.0	0.0
fatigue	2.7	4.6	1.7	3.0
peripheral edema	0.7	1.1	0.7	0.9
Central Nervous System				
dizziness	1.8	5.1	1.8	3.2
headache	4.7	4.5	2.7	0.4
Musculoskeletal				
muscle cramps	0.7	1.2	0.7	1.1
myalgia	1.4	2.4	0.0	0.0
Psychiatric				
insomnia	2.4	1.1	2.0	1.2
somnolence	0.7	1.1	0.7	0.9
loss of libido	1.2	0.4	1.2	0.4
impotence	0.7	1.1	0.7	1.1
Gastrointestinal				
diarrhea	1.4	4.3	1.2	1.1
nausea	0.9	1.1	0.9	0.9
dyspepsia	0.7	1.2	0.7	0.9

*Averages adjusted to combine across studies.
†Combined across studies.

Other adverse experiences that have been reported with the individual components are listed below.
Bisoprolol Fumarate: In clinical trials worldwide, a variety of other AEs, in addition to those listed above, have been reported. While in many cases it is not known whether a causal relationship exists between bisoprolol and these AEs, they are listed to alert the physician to a possible relationship. *Central Nervous System:* Unsteadiness, vertigo, syncope, paresthesia, hyperesthesia, sleep disturbance/vivid dreams, depression, anxiety/restlessness, decreased concentration/memory. *Cardiovascular:* Palpitations and other rhythm disturbances, cold extremities, claudication, hypotension, orthostatic hypotension, chest pain, congestive heart failure. *Gastrointestinal:* Gastric/epigastric/abdominal pain, peptic ulcer, gastritis, vomiting, constipation, dry mouth. *Musculoskeletal:* Arthralgia, muscle/joint pain, back/neck pain, twitching/tremor. *Skin:* Rash, acne, eczema, psoriasis, skin irritation, pruritus, purpura, flushing, sweating, alopecia, dermatitis, exfoliative dermatitis (very rarely). *Special Senses:* Visual disturbances, ocular pain/pressure, abnormal lacrimation, tinnitus, decreased hearing, earache, taste abnormalities. *Metabolic:* Gout. *Respiratory:* Asthma, bronchitis, dyspnea, pharyngitis, sinusitis. *Genitourinary:* Peyronie's disease (very rarely), cystitis, renal colic, polyuria. *General:* Malaise, edema, weight gain, angioedema.

In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents and should be considered potential adverse effects: *Central Nervous System:* Reversible mental depression progressing to catatonia, hallucinations, an acute reversible syndrome characterized by disorientation to time and place, emotional lability, slightly clouded sensorium. *Allergic:* Fever, combined with aching and sore throat, laryngospasm, and respiratory distress. *Hematologic:* Agranulocytosis, thrombocytopenia. *Gastrointestinal:* Mesenteric arterial thrombosis and ischemic colitis. *Miscellaneous:* The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with bisoprolol fumarate during investigational use or extensive foreign marketing experience.
Hydrochlorothiazide: The following adverse experiences, in addition to those listed in the above table, have been reported with hydrochlorothiazide (generally with doses of 25 mg or greater). *General:* Weakness. *Central Nervous System:* Vertigo, paresthesia, restlessness. *Cardiovascular:* Orthostatic hypotension (may be potentiated by alcohol, barbiturates, or narcotics). *Gastrointestinal:* Anorexia, gastric irritation, cramping, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, cholecystitis, sialadenitis, dry mouth. *Musculoskeletal:* Muscle spasm. *Hypersensitive Reactions:* Purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions. *Special Senses:* Transient blurred vision, xanthopsia. *Metabolic:* Gout. *Genitourinary:* Sexual dysfunction, renal failure, renal dysfunction, interstitial nephritis.

LABORATORY ABNORMALITIES

ZIAC: Because of the low dose of hydrochlorothiazide in ZIAC, adverse metabolic effects with B/H6.25 mg are less frequent and of smaller magnitude than with HCTZ 25 mg.

Treatment with both beta-blockers and thiazide diuretics is associated with increases in uric acid. Mean increases in serum triglycerides were observed in patients treated with bisoprolol fumarate and hydrochlorothiazide 6.25 mg. Total cholesterol was generally unaffected, but small decreases in HDL cholesterol were noted.

Other laboratory abnormalities that have been reported with the individual components are listed below.
Bisoprolol Fumarate: In clinical trials, the most frequently reported laboratory change was an increase in serum triglycerides, but this was not a consistent finding.

Sporadic liver test abnormalities have been reported. In the U.S. controlled trials experience with bisoprolol fumarate treatment for 4 to 12 weeks, the incidence of concomitant elevations in SGOT and SGPT of between 1 to 2 times normal was 3.9%, compared to 2.5% for placebo. No patient had concomitant elevations greater than twice normal.

In the long-term, uncontrolled experience with bisoprolol fumarate treatment for 6-18 months, the incidence of one or more concomitant elevations in SGOT and SGPT of between 1-2 times normal was 6.2%. The incidence of multiple occurrence was 1.9%. For concomitant elevations in SGOT and SGPT of greater than twice normal, the incidence was 1.5%. The incidence of multiple occurrences was 0.3%. In many cases these elevations were attributed to underlying disorders, or resolved during continued treatment with bisoprolol fumarate.

Other laboratory changes included small increases in uric acid, creatinine, BUN, serum potassium, glucose, and phosphorus and decreases in WBC and platelets. There have been occasional reports of eosinophilia. These were generally not of clinical importance and rarely resulted in discontinuation of bisoprolol fumarate.

As with other beta-blockers, ANA conversions have also been reported on bisoprolol fumarate. About 15% of patients in long-term studies converted to a positive titer, although about one-third of these patients subsequently reconverted to a negative titer while on continued therapy.
Hydrochlorothiazide: Hyperglycemia, glycosuria, hyperuricemia, hypokalemia and other electrolyte imbalances (see **PRECAUTIONS**), hyperlipidemia, hypercalcemia, leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, and hemolytic anemia have been associated with HCTZ therapy.

See **DOSAGE AND ADMINISTRATION** section in package insert for complete dosing and precautionary information.

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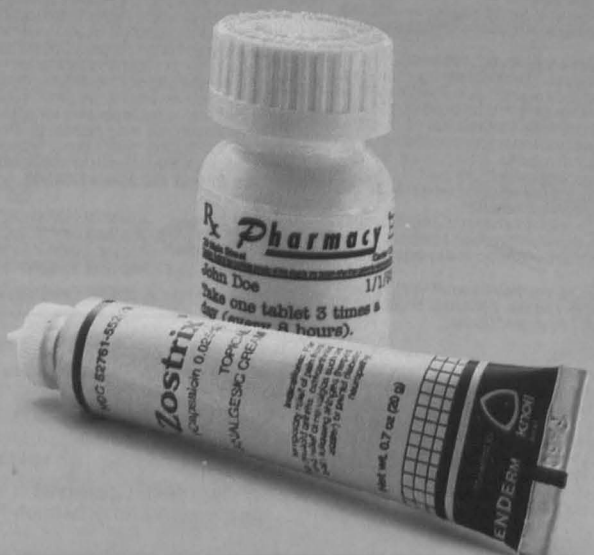
February 1994

8728-3R

Meeting the need for additional arthritis pain relief...

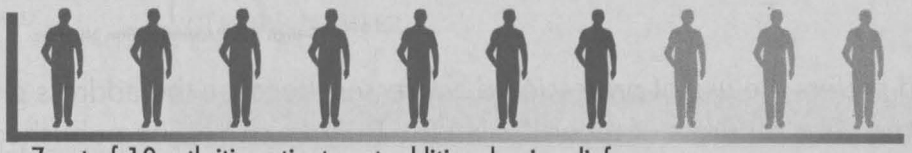
THE ADJUNCT TO NSAIDs THAT WORKS



ZOSTRIX® Works Jointly
(CAPSAICIN 0.025%)

A unique topical analgesic cream, ZOSTRIX has a mechanism of action that complements NSAIDs. NSAIDs inhibit prostaglandin synthesis, while capsaicin, the active ingredient in ZOSTRIX, depletes substance P, a neurotransmitter of pain.

When ZOSTRIX cream is added to NSAID therapy[1]:



—7 out of 10 arthritis patients get additional pain relief

—9 out of 10 patients experience improved mobility

ZOSTRIX® Works Directly
(CAPSAICIN 0.025%)

ZOSTRIX delivers pain-relieving action directly to the joint that hurts.[1,2] A new clinical study shows that application of capsaicin cream reduces the levels of substance P and other biochemical mediators in the synovial fluid of arthritic joints.[3]

ZOSTRIX® Works Safely and Economically
(CAPSAICIN 0.025%)

ZOSTRIX is free from systemic side effects, and has no known drug interactions. The most common side effect—transient burning at the site of application—usually resolves within a few days of use. When used properly, ZOSTRIX is inexpensive pain therapy. In fact, when treating a single knee joint, a 20-gm tube can last up to a month.

ZOSTRIX®

CAPSAICIN 0.025%

ADJUNCTIVE PAIN RELIEF FOR ALL YOUR ARTHRITIS PATIENTS

References:
1. Deal CL, Schnitzer TJ, Lipstein E, et al. Treatment of arthritis with topical capsaicin: a double-blind trial [subset analysis of data]. *Clin Ther.* 1991;13:383–395.
2. McCarthy GM, McCarty DJ. Effect of topical capsaicin in the therapy of painful osteoarthritis of the hands. *J Rheumatol.* 1992;19:604–607.
3. Lotz M, Weisman M, Yaksh T, Hagaman C, Flynn P. Effects of topical capsaicin (0.075%) on substance P and prostaglandin E_2 in synovial fluid: a double-blind study. *Arthritis Rheum.* 1992;35(9):S235.

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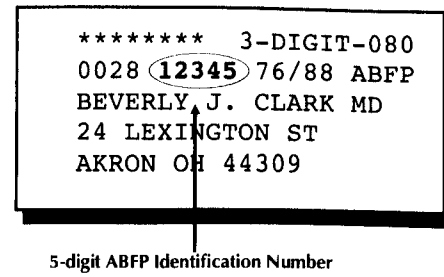

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Down it goes.

Clearly, the primary goal of antihypertensive therapy is to achieve target blood pressure control as uneventfully as possible.

Often, PLENDIL can help.

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

Just as importantly, PLENDIL is generally well tolerated when administered at recommended dosages.*

PLENDIL suits a wide range of hypertensive patients, including many with concomitant disorders, such as: hypercholesterolemia, diabetes, impaired renal function, COPD, and asthma.

PLENDIL. A calcium channel blocker for hypertension that is highly effective and usually well tolerated.

Use it alone. Or in combination with another antihypertensive agent.

Plendil®

(felodipine) *Tablets, 5 mg, 10 mg*

Because you consider the whole patient.

* Peripheral edema is the most common unwanted effect and is generally mild and age- and dose-related.

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

ASTRA/MERCK GROUP

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9

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 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* (Felodipine) 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.

ASTRA/MERCK GROUP

of MERCK & CO., INC.

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

Astra/Merck Group of Merck & Co., Inc.

725 Chesterbrook Boulevard, Wayne, PA 19087

PLENDIL is a product of Astra/Merck Research

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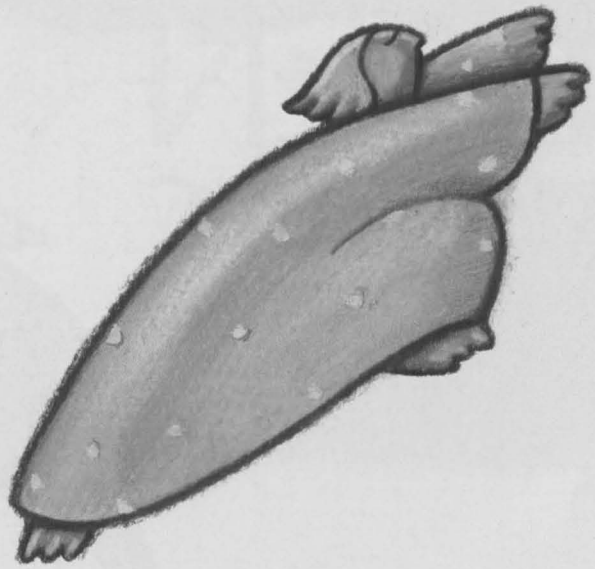
*Registered trademark of AB Astra

†Based on patient weight of 50 kg

The First in a New Chemical Class of Non-benzodiazepine Sleep Agents



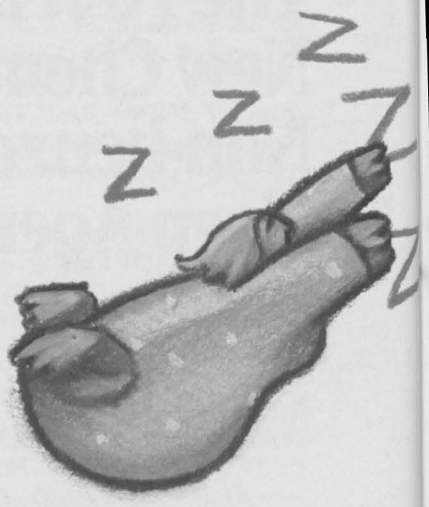
AMBIEN™

(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)
- Extensive clinical experience—over 500 million doses prescribed throughout Europe[1]

The First in a New Chemical Class of Non-benzodiazepine Sleep Agents



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

With AMBIEN, Patients Fall Asleep Fast and Get a Full Night's Sleep

- Rapid onset of action—sleep generally induced within 30 minutes[1-4]
- AMBIEN significantly increases duration of sleep[1,2,4,5]

AMBIEN Generally Preserves Normal Sleep Physiology[2-5]

Mean Percentage of Time in Each Sleep Stage[2]

	Stage 1	Stage 2	Stages 3&4	REM
AMBIEN	8.8%	56.5%	16.1%	18.6%
Natural Sleep	8.8%	56.7%	14.3%	20.5%

No statistically significant difference from natural sleep (at baseline) for all sleep stages, in a double-blind, controlled study of 12 healthy volunteers.[2] The clinical significance is unknown.

With AMBIEN, Patients Awaken Refreshed and Alert

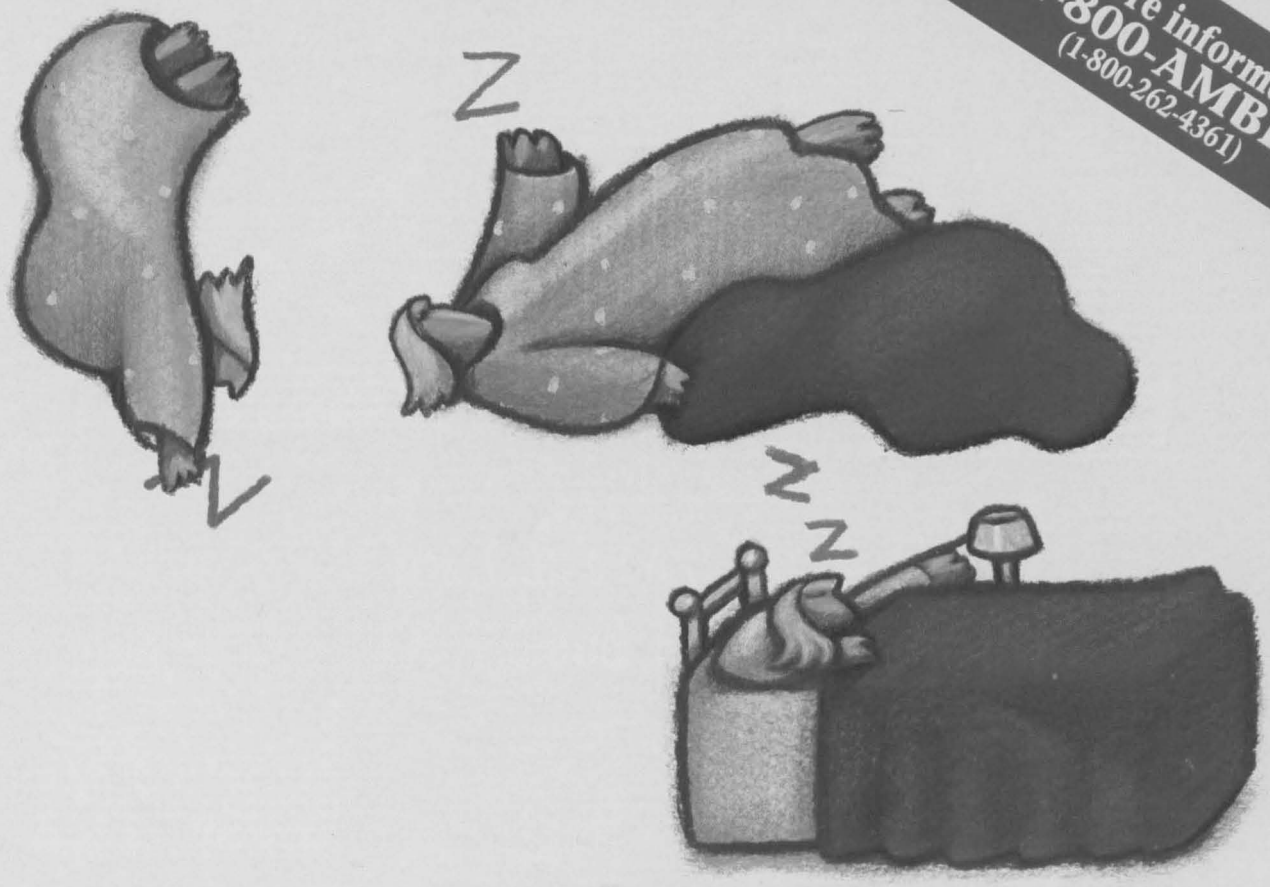
- A short half-life — mean 2.5 hours, with no active metabolites
- No evidence of significant daytime sedation or psychomotor impairment[1,2,5,6]

Although AMBIEN is generally not associated with next-day effects, until your patients know how they will react to this sleep agent, they should not engage in activities requiring mental alertness or motor coordination after taking AMBIEN (eg, driving or operating hazardous machinery). Potential impairment of the performance of such activities may occur the day following ingestion of AMBIEN.

SEARLE

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

For more information, call 1-800-AMBIEN-1 (1-800-262-4361)



A Favorable Safety Profile

- No rebound insomnia in studies of up to 35 nights at recommended doses[1-4]
- No evidence of tolerance in sleep latency in studies of up to 35 nights[1,3]
- 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%).

- Because of additive effects, AMBIEN should not be combined with alcohol. Dosage adjustments may be necessary when AMBIEN is coadministered with CNS depressants.

Recommended Dosage:

For adults:	one **10**-mg tablet
For elderly/debilitated patients:	one **5**-mg tablet

Patients should take AMBIEN right before going to bed and when ready for sleep.

- Prescriptions for AMBIEN should not exceed a 1-month supply. Hypnotics should generally be limited to 7 to 10 days of use, and reevaluation of the patient is recommended if they are taken for more than 2 to 3 weeks.
- In patients with hepatic dysfunction, dosage should be reduced and appropriate monitoring instituted.

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

The First in a New Chemical Class of Non-benzodiazepine Sleep Agents

AMBIEN
(ZOLPIDEM TARTRATE) C
5 MG & 10 MG TABLETS

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
Musculoskeletal System		
Myalgia	7	7
Arthralgia	4	4

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)
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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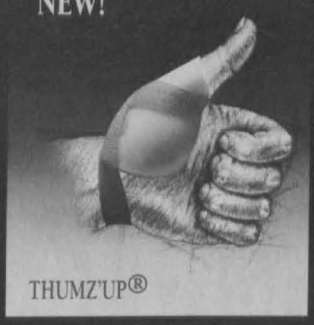
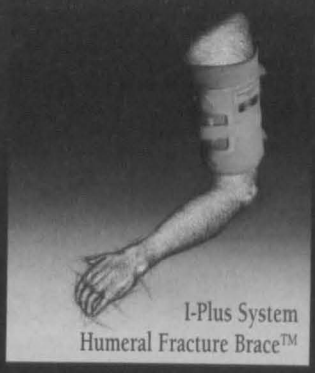
NEW!



THUMZ'UP®



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Humeral Fracture Brace™

Some People Say... "You Can't Get Too Much Of A Good Thing."

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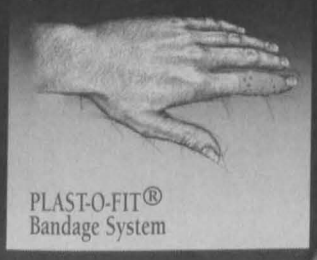

PLAST-O-FIT®
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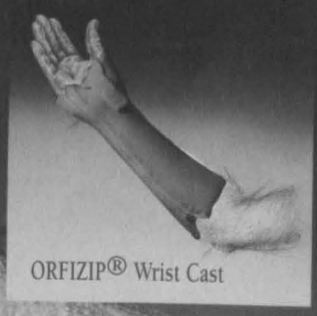

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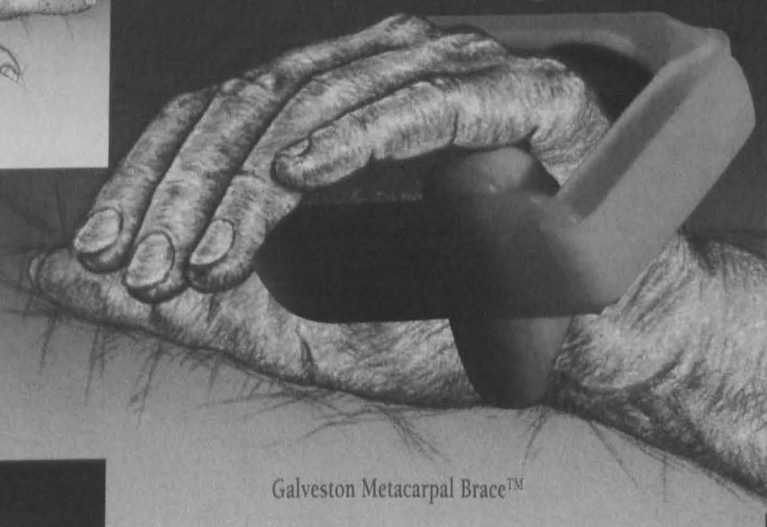

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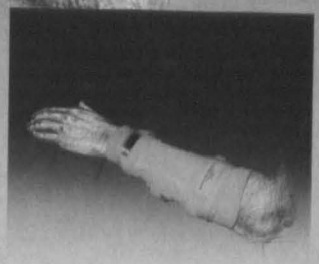
We Agree, And We Feel Your Patients Will Too.



I-Plus System
Ulnar Fracture Brace™

In 1987, Galveston Manufacturing introduced the Galveston Metacarpal Brace™. After over seven years of clinical use, the brace has proven successful in treating metacarpal shaft fractures. Galveston Manufacturing has continued serving the medical community, bringing you the latest quality fracture management products at affordable prices. So far this year we've introduced three new products to our line; the THUMZ'UP® functional thumb splint, the ORFIZIP® casting system and the PLAST-O-FIT® thermoplastic bandage system.

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MANUFACTURING

"Simple Solutions In Functional Bracing"

Go ahead.
Take a good hard look.

PLENDIL stands up to serious scrutiny.

Consider efficacy. PLENDIL provides a gradual onset of action for continuous 24-hour blood pressure control in many hypertensive patients. Alone or in combination with another antihypertensive agent.

Consider suitability. PLENDIL is appropriate for a wide range of patients, including many with concomitant disorders, such as: hypercholesterolemia, diabetes, impaired renal function, COPD, and asthma.

Consider safety. PLENDIL is generally well tolerated when administered at recommended dosages. Peripheral edema is the most common unwanted effect.*

Consider dosage. The vast majority of patients on PLENDIL receive prescriptions for 5 mg, once daily.†

So go ahead and measure its worth. Then give it serious consideration.

Plendil®

(felodipine) *Tablets, 5 mg, 10 mg*

Because you consider the whole patient.

*Peripheral edema is generally mild and age- and dose-related.

†1993 IMS NPA Prescription Data.

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

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

ASTRA/MERCK 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 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® (Felodipine) 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.

ASTRA/MERCK GROUP
of MERCK & CO., INC.

For more detailed information, consult your Astra/Merck Specialist or see complete Prescribing Information.
Astra/Merck Group of Merck & Co., Inc.
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PLENDIL is a product of Astra/Merck Research

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*Registered trademark of AB Astra
†Based on patient weight of 50 kg

The Journal of the American Board of Family Practice

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Issue Date	Closing Date
July-August	June 1
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Northeast

FAMILY PRACTITIONERS — Central New York State, BE/BC Family Practitioner for hospital-sponsored primary care clinic (OB not required). Excellent salary, malpractice, and hospital benefit package. Second Family Practitioner needed to activate solo practice with coverage. Send CV to: Oneida City Hospital Medical Staff Office, 321 Genesee Street, Oneida, NY 13421.

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COASTAL SOUTHERN MAINE & NEW HAMPSHIRE — Largest primary care group in state expanding — seeks additional BC/BE Family Practitioners in several of five multispecialty health center locations. Enjoy nearby ocean, mountains and lakes, plus social and cultural amenities. Progressive environment with emphasis on managed care offers teamwork, reasonable working hours, 1:4-5 call. Financial security of competitive salary, incentive bonus plan, excellent benefits package. Satisfy family needs for excellent education and safety of small city living with easy commute to Portland and Boston. *Great skiing, sailing, hiking and more.* Wonderful place to raise your children. Contact: Director of Corporate Recruitment, Martin's Point Health Care Center, 331 Veranda Street, PO Box 9746, Portland, ME 04104-5040; 800-348-9804.

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FALLON CLINIC — Join an expanding physician owned and directed 280-physician multispecialty group practice offering a wonderful opportunity to practice family medicine in the beautiful heart of Massachusetts. Competitive income and excellent benefits are offered. Please send CV to: Elizabeth Andreoli, Physician Services, The Fallon Clinic, Inc., 100 Central Street, Worcester, MA 01608, or call 800-635-1221, ext. 62275. Fax: 508-793-0909.

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POSITIONS AVAILABLE FULL/PART-TIME — For dedicated physicians with training in either Family Practice/Internal Medicine/ER Medicine. For family practice-urgent care centers in SW Florida. Physician friendly corporation consists of 4 urgent care centers with expanding opportunities. Goals are to provide wide range of services i.e.: continuity of care, industrial and family medicine, urgent care and even in-hospital privileges. Generous compensation/benefits. Ft. Myers is located on Florida's Gulf Coast between Sarasota and Naples and offers a variety of recreational and cultural activites. Send inquires to: Dr. Linda Saether, Medical Director, 13691 Metro Parkway, Suite 100, Ft. Myers, FL 33912 or fax CV to 813-768-5968.

"AMERICA'S MOST LIVABLE AREA" — As recently announced by Places Rated Almanac, invites you to explore the opportunity to practice family medicine with an exceptional primary care group. We are located in the Greater Cincinnati area which offers the best in lifestyles, education, housing, cultural amenities and leisure activities. Practice high quality family medicine in a progressive group of well-established physicians while earning an excellent income and positioning yourself for a secure future in the changing health care environment. For additional information contact: Mary Jo Stallings at St. Elizabeth Medical Center 800-765-4023.

ATLANTA, GEORGIA — FACULTY — FAMILY PRACTICE — Georgia Baptist Medical Center. Family Practice Residency Program, 1000 Corporate Center Drive, Suite 200, Morrow, GA 30260. 404-968-6464 or 800-851-1078. Fax: 404-968-6455. The Opportunity: Georgia Baptist Medical Center, a 523-bed tertiary care facility, affiliated with the Medical College of Georgia, is actively recruiting a BC/BE Family Practice Physician for a faculty position with the Family Practice Residency Program, located in Morrow, Georgia (17) miles south of downtown Atlanta. Candidates must hold an MD degree and be board certified or eligible in family practice and do OB. The residency program is procedurally oriented, therefore applicants should possess strong clinical skills and dynamic teaching abilities. Responsibilities include precepting residents and inpatient and outpatient care. The Community: Atlanta, population 2.8 million is located in North Central Georgia. Atlanta's geographic location offers a comfortable lifestyle, affordable housing, with a blend of rural beauty and urban accessibility. The area also offers numerous outdoor activities, universities, four star restaurants, cultural amenities and major league sporting events (Braves, Hawks and Falcons). Compensation: Competitive salary, malpractice insurance, health and dental insurance, long term disability, retirement program, CME stipend and allocated time off, tax sheltered annuities.

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- Obstetrics preferred for Residency Faculty position; optional for community clinics

If this sounds like what you are looking for, and you are ready to join an energetic team, please ask for more information by contacting:

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Director, Family Practice Residency Programs
P.O. Box 81611, Salinas, CA 93912
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Midwest

AMBULATORY CARE CENTER — Group seeks full-time physician to practice in two ambulatory care centers in Bloomington, Indiana. Competitive salary and full range of benefits. Scenic southern Indiana area includes Indiana University, Hoosier National Forest, numerous lakes and exceptional cultural opportunities. Contact: Ruth Barrett at 812-332-3443.

UNIVERSITY OF WISCONSIN DEPARTMENT OF FAMILY MEDICINE — MILWAUKEE FACULTY POSITIONS — ST. LUKE'S FAMILY PRACTICE RESIDENCY — Residency Director — Successful 24-resident program, 8 full-time faculty, new FPC at excellent 600-bed community hospital seeks energetic director for opportunity to further develop program within large health care system. Active community outreach with potential for further expansion. Extremely supportive environment fostering educational innovation. Full-time UW faculty appointment. Assistant Director — MD faculty sought for new ninth faculty position at Assistant or Associate Professor level. Position involves patient care/teaching/academics in negotiable amounts. Obstetrics strongly preferred. Address inquiries to: N. Turkal, MD, St. Luke's Family Practice Center, 2901 West Kinnickinnic River Parkway, #175, Milwaukee, WI 53215; 414-649-6723. The University of Wisconsin is an Equal Opportunity/Affirmative Action Employer.

MINNESOTA EMERGENCY MEDICINE OPPORTUNITIES — Excellent full-time staff positions are available at community hospitals in Hibbing, Morris, Winona, and Fairmont. These emergency departments have annual volumes of 6,000 to 12,000. We offer competitive remuneration and participation in occurrence malpractice insurance. We are also seeking a Medical Director for Fairmont, Minnesota. Medical Directors receive an additional annual stipend for administrative duties, plus full benefits, including participation in a 401K plan after one year of service. For more information, please call: Linda Beery, Spectrum Emergency Care 800-325-2716 or FAX your CV to Linda at 314-579-1374.

ST. LOUIS — Premier group is seeking BC/BE physicians in family practice. This is an excellent opportunity for the physician who wants to concentrate on patients, not paperwork. Excellent salary, bonus, good call schedule, paid malpractice, vacation, CME and an outstanding 401K. Send CV to: Rick Klos, Group Health Plan, 940 West Port Plaza, St. Louis, MO 63146 or call 800-743-3901.

HOSPITAL BASED PHYSICIAN — BCN-Health Central is seeking a hospital based physician to direct, manage and coordinate all clinical services for the plan hospitalized patients. Physician must be board certified or eligible in either internal medicine or family practice and have previous experience in a critical care hospital setting. Physician must have strong clinical skills with the ability to provide clinical supervision. Effective interpersonal skills for communication with patients, families, specialists, hospital staff and continuing care nurses. If interested, submit resume to: Physician Recruitment Manager, Blue Care Network-Health Central, 1403 South Creyts Road, Lansing, MI 48917. Blue Care Network-Health Central is committed to continuous quality improvement, appreciating and valuing the diversity of our workforce and the communities which we serve and the fulfillment of Equal Employment Opportunity.

TOLEDO, OHIO — FAMILY PRACTICE — BE/BC FP for group practice. 1-in-3 coverage. Outstanding salary and benefits. Send CV to: Jules Ehrenberg, E.J. Michaels, 1865 Palmer Avenue, Larchmont, NY 10538; call 914-833-1700, outside the New York metropolitan area 800-333-2999, fax 914-833-1711.

FAMILY PRACTICE PHYSICIAN FACULTY (ABFP) POSITION — For expanding urban residency and medical student teaching program in inner-city Detroit. Model ambulatory and community hospital settings, diverse cultural populations, progressive practice and curriculum, community-oriented primary care. Academic affiliation and appointments with Case Western Reserve University. Committed to service and teaching for underserved. Obstetrics preferred. Opportunities include leadership, professional development, research. Excellent salary and benefits. Henry Ford Health System is an Equal Opportunity Employer. Send curriculum vitae to: Susan Schooley, MD, Chairman, Department of Family Medicine, Henry Ford Health System, One Unisys Place, Room 1C63, Detroit, MI 48202; 313-874-5373, 313-874-5381 FAX.

PRACTICE FAMILY MEDICINE AND STILL ENJOY FAMILY TIME — MedOHIO Physician Care Centers, located throughout Columbus, Ohio, currently have opportunities available for Family Practice, Internal Medicine Pediatric and Internal Medicine physicians. As part of The Ohio State University Medical Center, the MedOHIO system offers you the chance to develop your practice without the hassles of overhead, employee management or capital expenses. MedOHIO also has complete access to The Ohio State University Medical Center's resources, experts, and tertiary care facilities. Columbus is a family-friendly city with excellent schools, affordable housing and a secure environment. If you're interested in practicing family medicine and still having time for your own family, call: 614-293-3729 and ask for Dr. Deborah Cole-Sedivy, Medical Director, or Jim Guidry, Director of Operations, for MedOHIO Physician Care Centers.

FAMILY PRACTICE PHYSICIAN FACULTY (ABFP) POSITION — For expanding urban residency and medical student teaching program in inner-city Detroit. Model ambulatory and community hospital settings, diverse cultural populations, progressive practice and curriculum, community-oriented primary care. Academic affiliation and appointments with Case Western Reserve University. Committed to service and teaching for underserved. Obstetrics preferred. Opportunities include leadership, professional development, research. Excellent salary and benefits. Henry Ford Health System is an Equal Opportunity Employer. Send curriculum vitae to: Susan Schooley, MD, Chairman, Department of Family Medicine, Henry Ford Health System, One Unisys Place, Room 1C63, Detroit, MI 48202; 313-874-5373, 313-874-5381 FAX.

FACULTY POSITION — KANSAS CITY — Baptist Medical Center in Kansas City, a well-established, highly successful and progressive community program has a full-time faculty position for an experienced board certified Family Practitioner. Four years of clinical experience is preferred. Responsibilities include: supervising residents in our model unit, attending on inpatient rounds every fourth week, and approximately 40% direct patient care time. OB is optional, call involves morning rounds every 4th-6th weekend. As usual, we have a full complement of 24 excellent residents. We are known for our quality, friendly atmosphere and participative management style. Salary and benefits are competitive. The metropolitan area of Kansas City, Missouri with over 1.6 million people offers very affordable housing, excellent schools and universities, many cultural amenities, major league sports and a very diversified economic base. Call today — or fax your CV to: Larry Rues, MD, Program Director, Goppert Family Care Center, 6601 Rockhill Road, Kansas City, MO 64131. Phone: 816-276-7650. Fax: 816-926-2274.

UNIVERSITY OF WISCONSIN DEPARTMENT OF FAMILY MEDICINE — MILWAUKEE FACULTY POSITION — SINAI SAMARITAN FAMILY CARE CENTER — Leadership Faculty Member — Initially, Associate Director sought for development/implementation of urban track of well established 24-resident St. Luke's Family Practice Residency program at Sinai Samaritan Family Care Center. Option to develop full Family Practice residency. 4 family practitioners currently practice/teach at this urban center. St. Luke's and Sinai Samaritan are part of a large/very supportive health care system in Eastern Wisconsin. Position includes administration, patient care, teaching and academic endeavors. Full-time UW faculty appointment at Assistant or Associate Professor level. Community Medicine/urban practice background preferred. Address inquiries to: N. Turkal, MD, St. Luke's Family Practice Center, 2901 West Kinnickinnic River Parkway, #175, Milwaukee, WI 53215; 414-649-6723. The University of Wisconsin is an Equal Opportunity/Affirmative Action Employer.

Southwest

COME SEE THE SOUTH! — Family Practitioner needed to take the place of a retiring physician and join this fabulous 40 physician group. Generous financial package including - income guarantee with 100% production incentive bonus; malpractice; profit share; and much more. No business hassles and a ready made practice. You can't afford to let this opportunity get away! Call: Dirk Smith at 800-705-7055. Fax: 214-401-0337.

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$140,000 MINIMUM EARNINGS/FAMILY PRACTICE — within one hour from San Antonio, Texas; soft rolling hills, 80 miles from Gulf Coast. Excellent dove and quail hunting, top rated public/private schools, 6 major lakes. 46-bed hospital, no OB, contracted ER, beautiful office building, no risk income guarantee. **Call Chris Mileger at Ext. #3-252.**

MIDWEST COLLEGE TOWN — 1:6 call, existing group practice, $45,000 in signing bonuses, salary, benefits, production bonus. $25,000-$30,000 per year medical loan repayment. While being located in a town with 4000 students, indoor track, racquetball, swimming pool, planetarium, yearly golf open, country fairs, fitness trails, cross-country skiing, hunting, and *top* schools. I've assessed approximately 250 cities and this one is a top find. **Call David Reeves at Ext. #3-468.**

SOUTHWEST — THIS PRACTICE HAS IT ALL: $150,000 package. Very limited inpatient. No management hassles. No billing or collection responsibility. No more than one weekend per month on call. Live in national forest area with unlimited fishing, hunting, camping, and boating. Fantastic benefits including housing. **Call David Townsend at Ext. #3-352.**

LOUISIANA/FAMILY PRACTITIONER NEEDED BY PROGRESSIVE AND GROWING GROUP. $150,000 guaranteed, 1:3-1:4 call, no OB. Excellent schools, golf, country club, and 2 area lakes known for its fishing and hunting. State-of-the-art, solid 102-bed acute care facility located just 45 minutes from a major metropolitan area. **For complete details call Mike Garvey, Ext. #3-361.**

For More Details Contact Our Southwest Region

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For more information about family practice opportunities with our innovative organization send your CV to:

Karen Elbert
Grand Valley Health Plan
829 Forest Hill SE
Grand Rapids, MI 49546
(616)949-2310

PROFESSOR AND HEAD — Louisiana State University School of Medicine - New Orleans announces the opening of the search for the Professor and Head of the Department of Family Medicine. The Lousiana State University School of Medicine, Department of Family Medicine has become recognized for excellence in education. Student teaching and faculty practice are the major aspects of the current department. Much opportunity for growth exists in the New Orleans Programs and in two major affiliates in Baton Rouge and Lafayette. A Center of Excellence in Primary Care is being developed in Baton Rouge with a strong base in family practice. Salary and academic rank are commensurate with experience and qualifications. Interested individuals should send a cover letter expressing their interest in the position, and a recent copy of their curriculum vitae. AA/EOE. Thomas E. Elkins, MD, Search Committee for Family Medicine, Louisiana State University, School of Medicine - New Orleans, 1542 Tulane Avenue, Room 550, New Orleans, LA 70112.

THE UNIVERSITY OF ARKANSAS HEALTH CENTER — Is seeking a board-certified physician to serve students and employees in the ambulatory care clinic. Eligibility for medical licensure in Arkansas, experience in general medicine required; interest in women's issues and patient education preferred. A 12 month position with a full complement of benefits, application review will begin June 1 and will continue until position is filled. To apply, send letter of interest, current resume, three letters of recommendation to: Physician Search Committee, University of Arkansas Health Center, 600 Razorback Road, Fayetteville, AR 72701. Women and minorities are encouraged to apply. UOA is an AA/EOE Employer.

SUNNY SOUTH — Two Family Practice opportunities. $130,000 net income guarantee plus generous bonus structure. $15,000 signing bonus, and all relocation expenses. Call 1-5. No management responsibilities. Excellent hospital administration and staff support. Reply: Michael Tanguay, Nova HealthCare, 14881 Quorum Drive, Suite 310, Dallas, TX 75240, 800-330-6682.

FAMILY PRACTICE — OSHKOSH, WISCONSIN — Well-established group of four Family Practitioners is recruiting two additional FPs. Busy practice with the full range of clinical services. OB is optional. Competitive financial package and fringe benefits. Oshkosh is an attractive community of 55,000 people (metro area of 350,000), located on the shores of Lake Winnebago and in the heart of Wisconsin's beautiful Fox River Valley. 90 minutes north of Milwaukee. University of 12,000 students. Good schools. Close proximity to outdoor sports and nature. Low crime area. Send CV to: Christopher Kashnig, Mercy Medical Center, 631 Hazel Street, Oshkosh, WI 54902. Call: 414-236-2430. Fax: 414-236-1312.

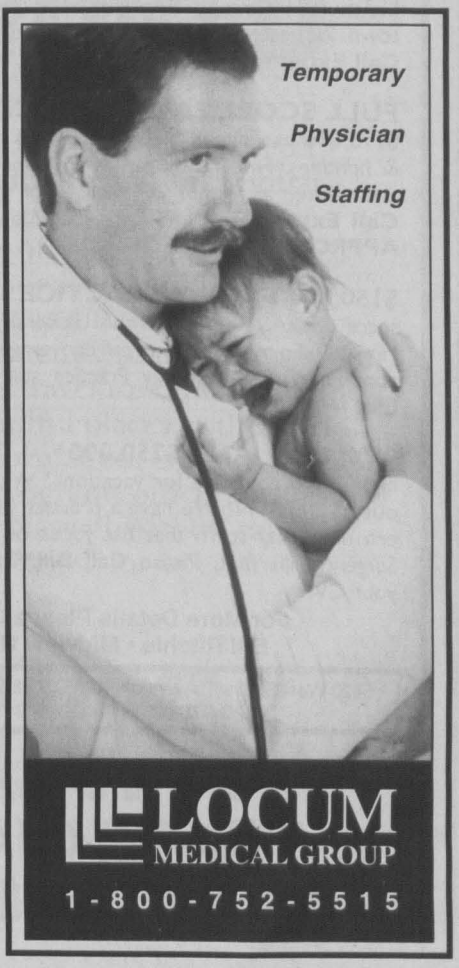
OCHSNER MEDICAL INSTITUTIONS — Are actively recruiting additional BC/BE Family Practitioners for expanding departments at the Ochsner Clinic Slidell, Ochsner Clinic Mandeville, Ochsner Clinic Lapalco, and Ochsner Clinic Baton Rouge. Excellent and unique opportunity to become a part of the preeminent multispecialty group practice in the Gulf South. Ochsner physicians receive a competitive salary, liberal fringe benefits package, generous paid CME and vacation time, excellent retirement package, and opportunity for partnership status. New Orleans, Baton Rouge, and the cities' surrounding areas offer many cultural and recreational activities for the single physician or for the entire family. Send CV to: Ochsner, Physician Recruiting, Ref# A22FP, 16777 Medical Center Drive, Baton Rouge, LA 70816. 800-488-2240.

BEHAVIORAL MEDICINE

FACULTY POSITION
PHOENIX, AZ

St. Joseph's Hospital & Medical Center, a large multi-specialty teaching hospital, is seeking a Behavioral Medicine Faculty Member to join our Family Practice Residency Program that is affiliated with the University of Arizona. You will have a variety of clinical, administrative and educational opportunities. Phoenix offers a major metropolitan atmosphere with year-round recreational activities. For more information, send your C.V. to: **Donald E. McHard, M.D., Director, St. Joseph's Family Practice Residency, 2927 N. 7th Ave., Phoenix, AZ 85013;** or call **(602) 285-3153.** EOE.

St. Joseph's Hospital and Medical Center
Mercy Healthcare Arizona



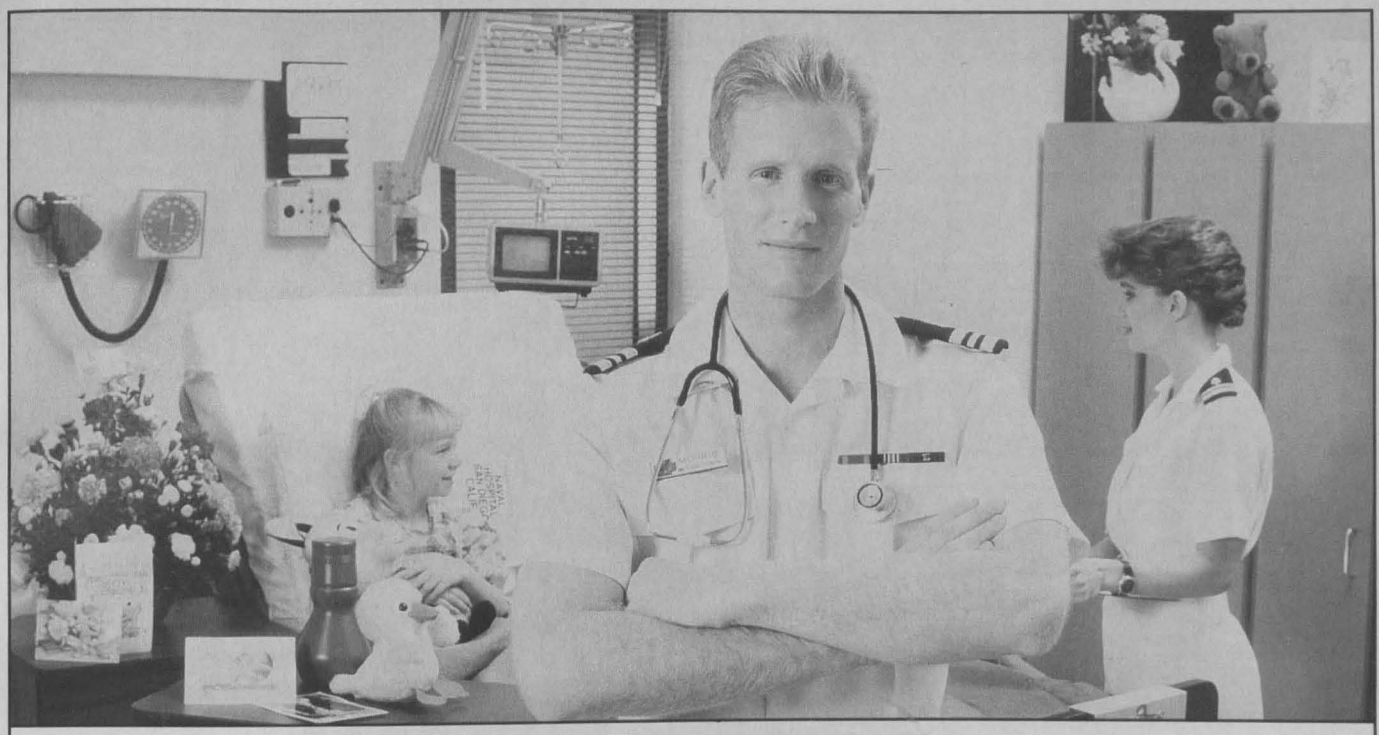
PENSACOLA, FL — Numerous opportunities for BC/BE Family Practitioners in this Gulf-Coast community. Various positions available ranging from employment to single-specialty group practice. Excellent salaries, opportunities for professional growth, and unsurpassed quality of life. Wonderful recreational activities including sailing, water-sports, fishing, golf, and sugar-white beaches! For more information, please contact: Mark Faulkner, Director of Physician Relations at 800-432-4654 (in FL) or 800-874-1556 (outside FL).

West

FAMILY PRACTITIONER — Multispecialty group in Sioux Falls, South Dakota, a city recently rated as one of the most desirable places to live in the nation, is looking for a board certified/board eligible Family Practitioner. Attractive salary and benefits. Send CV to: Medical Director, Central Plains Clinic, 1100 East 21st Street, Sioux Falls, SD 57105.

Pacific

SAN FRANCISCO BAY AREA — FAMILY PRACTICE — BC/BE — Continued growth in 130+ physician, multispecialty group, has resulted in immediate need for BC/BE, residency-trained, Family Practice physicians in several locations. Superb opportunity to join 22 FPs in busy clinic. No obstetrics. Sunnyvale Medical Clinic is a highly respected medical group dedicated to providing quality health care to the communities of the south San Francisco Bay Area. Competitive salary, benefit and incentive programs, 18 months to shareholder status. If you are interested in being part of this dynamic, growing team, please mail or fax your CV and references to: Sunnyvale Medical Clinic, Inc., Kathleen Strawbridge, Medical Staff Coordinator, Box 3496, Sunnyvale, CA 94088-3496. Fax: 408-735-1472.



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You'll work in clinical settings in the United States and around the world with top professionals and state-of-the-art equipment and facilities. Through funded continuing education and specialty training, you'll have the opportunity to develop your full professional potential as well as the freedom to move from practice to research or teaching without losing seniority, salary level or retirement benefits.

You'll earn an excellent starting salary based on your credentials and years of experience, and federal law provides free medical liability protection to Navy physicians. You may also be entitled to special pay in addition to your regular salary and allowances. Navy benefits include 30 days of paid vacation earned each year, free medical and dental care, tax-free housing and food allowance, an excellent retirement system and opportunities for free travel to some of the most exotic and beautiful places in the world.

For more information, contact your local Navy Medical Programs officer, or if you'd like to talk to a Navy physician, call **1-800-USA-NAVY.** Ask for operator 10.

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References: 1. Laska EM, Sunshine A, Meller F et al. Caffeine as an analgesic adjuvant. *JAMA*. 1984;251:1711-18. **2.** Benson GD. Hepatoxicity following the therapeutic use of antipyretic analgesics. *Am J Med*. 1983;75(suppl 5A):85-93. **3.** Jick H. Effects of aspirin and acetaminophen in gastrointestinal hemorrhage. *Arch Intern med*. 1981;141:316-321. **4.** Mielke CH Jr. Comparative effects of aspirin and acetaminophen on hemostasis. *Arch Intern Med*. 1981:305-310. **5.** Hansten PD. *Drug Interactions, ed. 5*. Philadelphia: Lea & Febiger, 1985, p. 95.

ESGIC-PLUS™

Tablets (Butalbital, Acetaminophen and Caffeine Tablets, USP)
50mg/500mg/40mg

Brief Prescribing Information: (Please see package insert for full prescribing information)

DESCRIPTION: Each ESGIC-PLUS™ tablet for oral administration contains:

Butalbital*	50 mg
*WARNING: May be habit forming	
Acetaminophen	500 mg
Caffeine	40 mg

CLINICAL PHARMACOLOGY: Pharmacologically, ESGIC-PLUS™ combines the analgesic properties of acetaminophen-caffeine with the anxiolytic and muscle relaxant properties of butalbital.

CONTRAINDICATIONS: Hypersensitivity to acetaminophen, caffeine, or barbiturates. Patients with porphyria.

PRECAUTIONS: General: Barbiturates should be administered with caution, if at all, to patients who are mentally depressed, have suicidal tendencies, or a history of drug abuse.

Elderly or debilitated patients may react to barbiturates with marked excitement, depression, and confusion. In some persons, barbiturates repeatedly produce excitement rather than depression.

Drug Interactions: Patients receiving narcotic analgesics, antipsychotics, anti-anxiety agents, or other CNS depressants (including alcohol) concomitantly with ESGIC-PLUS™ (Butalbital, Acetaminophen, and Caffeine) may exhibit additive CNS depressant effects.

Drugs	Effect
Butalbital with coumarin anticoagulants	Decreased effect of anticoagulant because of increased metabolism resulting from enzyme induction.
Butalbital with tricyclic antidepressants	Decreased blood levels of the antidepressant.

Usage in Pregnancy: Adequate studies have not been performed in animals to determine whether this drug affects fertility in males or females, has teratogenic potential or has other adverse effects on the fetus. There are no well-controlled studies in pregnant women. Although there is no clearly defined risk, one cannot exclude the possibility of infrequent or subtle damage to the human fetus. ESGIC-PLUS™ should be used in pregnant women only when clearly needed.

Nursing Mothers: The effects of ESGIC-PLUS™ on infants of nursing mothers are not known. Barbiturates are excreted in the breast milk of nursing mothers. The serum levels in infants are believed to be insignificant with therapeutic doses.

Pediatric Use: Safety and effectiveness in children below the age of 12 have not been established.

ADVERSE REACTIONS: The most frequent adverse reactions are drowsiness and dizziness. Less frequent adverse reactions are lightheadedness and gastrointestinal disturbances including nausea, vomiting and flatulence. Mental confusion or depression can occur due to intolerance or overdosage of butalbital.

Several cases of dermatological reactions including toxic epidermal necrolysis and erythema multiforme have been reported.

DRUG ABUSE & DEPENDENCE: Prolonged use of barbiturates can produce drug dependence, characterized by psychic dependence and tolerance. The abuse liability of ESGIC-PLUS™ is similar to that of other barbiturate-containing drug combinations. Caution should be exercised when prescribing medication for patients with a known propensity for taking excessive quantities of drugs, which is not uncommon in patients with chronic tension headache.

OVERDOSAGE: The toxic effects of acute overdosage of ESGIC-PLUS™ are attributable mainly to its barbiturate component, and, to a lesser extent, acetaminophen. Because toxic effects of caffeine occur in very high dosages only, the possibility of significant caffeine toxicity from ESGIC-PLUS™ overdosage is unlikely.

Barbiturate: Signs and Symptoms: Drowsiness, confusion, coma; respiratory depression; hypotension; shock.

Treatment:

1. Maintenance of an adequate airway, with assisted respiration and oxygen administration as necessary.
2. Monitoring of vital signs and fluid balance.
3. If the patient is conscious and has not lost the gag reflex, emesis may be induced with ipecac. Care should be taken to prevent pulmonary aspiration of vomitus. After completion of vomiting, 30 grams of activated charcoal in a glass of water may be administered.
4. If emesis is contraindicated, gastric lavage may be performed with a cuffed endotracheal tube in place with the patient in the facedown position. Activated charcoal may be left in the emptied stomach and a saline cathartic administered.
5. Fluid therapy and other standard treatment for shock, if needed.
6. If renal function is normal, forced diuresis may aid in the elimination of the barbiturate. Alkalinization of the urine increases renal excretion of some barbiturates, especially phenobarbital.
7. Although not recommended as a routine procedure, hemodialysis may be used in severe barbiturate intoxication or if the patient is anuric or in shock.

Acetaminophen: Signs and Symptoms: In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams and fatalities with less than 15 grams. Importantly, young children seem to be more resistant than adults to the hepatotoxic effect of an acetaminophen overdose.

Early symptoms following a potentially hepatotoxic overdosage may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may be apparent until 48 to 72 hours post-ingestion.

Treatment: The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. Patients' estimates of the quantity of a drug ingested are notoriously unreliable. Therefore, if an acetaminophen overdose is suspected, a serum acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. Liver function studies should be obtained initially and repeated at 24-hour intervals.

The antidote, N-acetylcysteine, should be administered as early as possible, preferably within 16 hours of the overdose ingestion for optimal results, but in any case, within 24 hours. Following recovery, there are no residual, structural or functional hepatic abnormalities.

DOSAGE AND ADMINISTRATION: Oral: One ESGIC-PLUS™ tablet every four hours as needed. Do not exceed six tablets or capsules per day.

HOW SUPPLIED: ESGIC-PLUS™ (Butalbital* 50 mg [*WARNING—May be habit forming], Acetaminophen 500 mg and Caffeine 40 mg) Tablets are white, capsule-shaped, single-scored, and are debossed "FOREST" on the upper side, "678" on one side of the score on the lower side. They are supplied as: Bottles of 100—NDC 0456-0678-01.

Storage: Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

Dispense in a tight, light-resistant container with a child-resistant closure.

CAUTION: Federal law prohibits dispensing without prescription.

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