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

ZIAC™

(bisoprolol fumarate-hydrochlorothiazide)

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

First-line therapy option

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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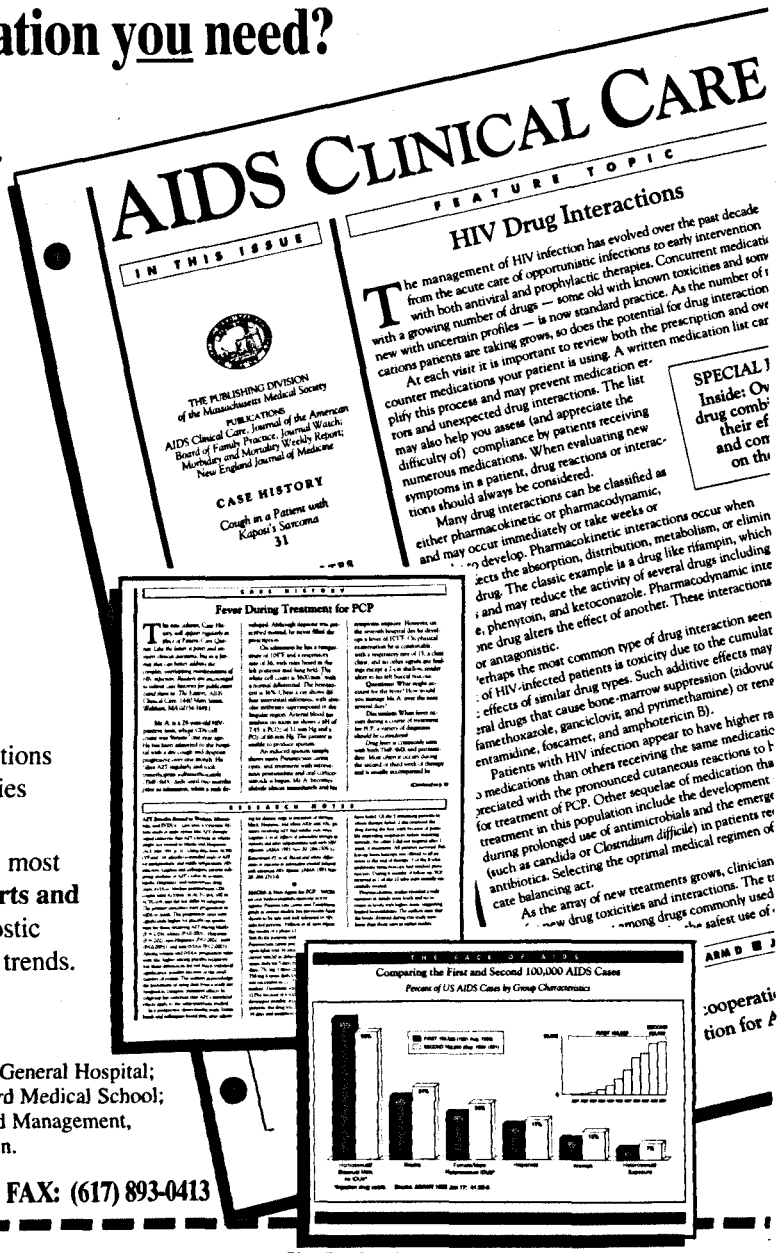

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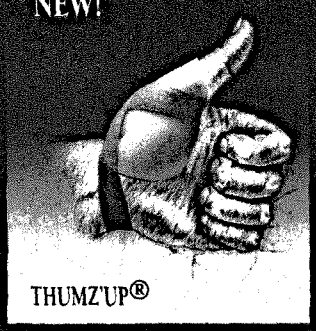

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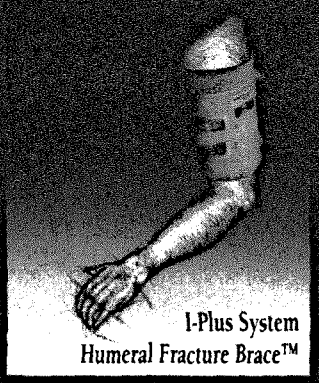

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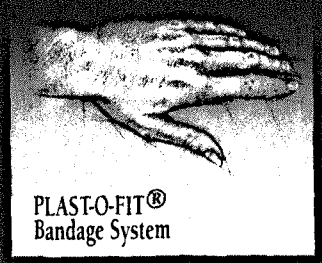

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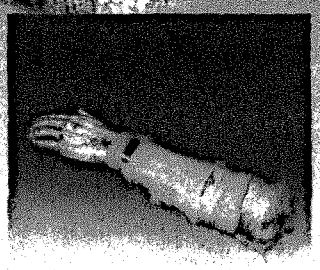

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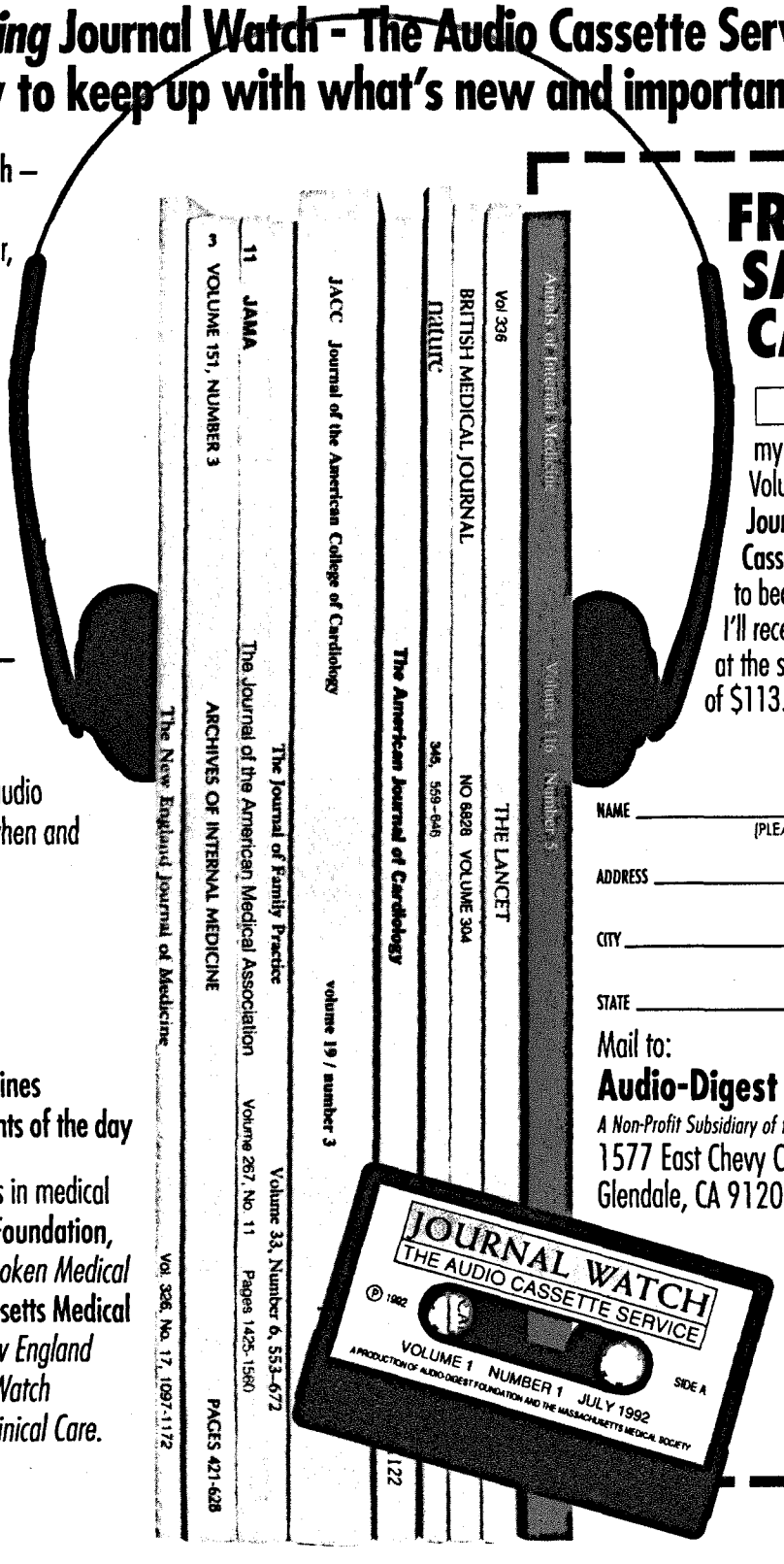

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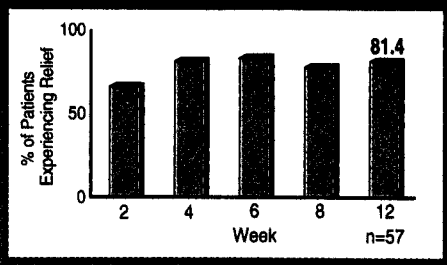

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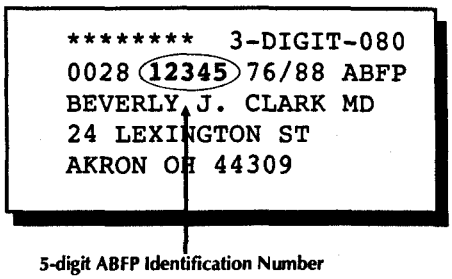

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The *Journal of the American Board of Family Practice* welcomes for editorial review manuscripts that contribute to family practice as a clinical scientific discipline. High priority is given to reports of clinically relevant studies that have practical implications for improved patient care. Manuscripts are considered in relation to the extent to which they represent original work, their significance to the advancement of family medicine, and their interest to the practicing family physician. Some papers that are accepted by the *Journal* will be selected for an accompanying guest editorial or concurrent commentary by other invited authors addressing issues raised by the papers. The *Journal* publishes the following features:

Original Articles. Reports of original research, usually dealing with a clinical, health services, or other clinically relevant study.

Medical Practice. Scholarly articles that relate directly to clinical topics useful in everyday family practice, whether dealing with diagnostic or therapeutic roles of the family physician or reporting studies of what family physicians do in practice.

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The following guidelines are in accordance with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals." The current (fourth) edition was published in the February 7, 1991, issue of the *New England Journal of Medicine.*

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With the manuscript, provide a page giving the title of the paper; a running foot of fewer than 40 letter spaces; the name(s) of the author(s), including first name(s) and academic degree(s); the name of the department and institution in which the work was done; and the name and address of the author to

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Use another page to provide an abstract of not more than 200 words. This abstract should be factual, not descriptive, with its content appropriate to the type of paper. For original articles reporting results of studies, a four-paragraph format should be used labeled Background, Methods, Results, and Conclusions. These should briefly describe, respectively, the object of the study, the methods used, the major results, and the author(s) conclusions. Abstracts are not necessary for Brief Reports or World Perspective papers.

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Except for units of measurement, abbreviations are discouraged. Consult the *Council of Biology Editors Style Manual* (Fifth edition. Bethesda, MD: Council of Biology Editors, 1983) for lists of standard abbreviations. The first time an abbreviation appears, it should be preceded by the words for which it stands.

Drug Names

Generic names should, in general, be used. If an author so desires, brand names may be inserted in parentheses.

Inclusive Language

Sex bias should be avoided and gender-inclusive language used whenever possible.

References

References must be typed in double spacing and numbered consecutively as they are cited. References first cited in tables or figure legends must be numbered so that they will be in sequence with references cited in the text. The style of references is that of the *Index Medicus*. List all authors when there are 6 or fewer; when there are 7 or more, list the first 6, then "et al." Sample references are as follows:

Standard Journal Article

(List all authors, but if the number exceeds 6, give 6 followed by et al. Note that month and issue number are omitted when a journal has continuous pagination throughout a volume.)

Morrow JD, Margolies GR, Rowland J, Roberts LJ 2nd. Evidence that histamine is the causative toxin of scombroid-fish poisoning. N Engl J Med 1991; 324:716-20.

Organization as Author

Clinical Experience Network (CEN). A large-scale, office-based study evaluates the use of a new class of nonse dating antihistamines. A report from CEN. J Am Board Fam Pract 1990; 3:241-58.

Book

Rakel RE. Textbook of family practice. 4th ed. Philadelphia: WB Saunders, 1990.

Chapter in Book

Haynes RC Jr. Agents affecting calcification: calcium, parathyroid hormone, calcitonin, vitamin D, and other compounds. In: Gilman AG, Rall TW, Nies AS, Taylor P, editors. Goodman and Gilman's the pharmacological basis of therapeutics. 8th ed. New York: Pergamon Press, 1990.

Government Agency

Schwartz JL. Review and evaluation of smoking cessation methods: the United States and Canada, 1978-1985. Bethesda, MD: Department of Health and Human Services, 1987. (NIH publication no. 87-2940.)

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Handle with care.

The value of treating hypertension in older patients has been clearly established.*[1] Today, the prevalence of hypertension in people over 60 is greater than 60%.[2]

Often, PLENDIL represents a good choice for older patients with hypertension.†

With a simple once-daily dosage regimen, PLENDIL provides a gradual onset of action with continuous 24-hour control. Generally, PLENDIL is well tolerated when administered in recommended doses.‡

Usual dosage range is 5 mg to 10 mg daily. But, patients over 65 may have elevated plasma concentrations of felodipine, and may therefore respond to lower doses of PLENDIL.

PLENDIL. A considerate choice for patients who deserve "special handling."

* The ability of calcium channel blockers to reduce morbidity or mortality has not been established.

† Patients over 65, and those with impaired liver function, should have their blood pressure monitored closely during adjustment of PLENDIL and should rarely require doses above 10 mg. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION in the Prescribing Information.)

‡ Peripheral edema, generally mild, is the most common adverse experience. PLENDIL is contraindicated in patients who are hypersensitive to this product.

Plendil®

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

Because you consider the whole patient.

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

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FRASER

References:

1. *The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.* Bethesda, MD: National Heart, Lung, and Blood Institute; 1993. NIH Publication No. 93-1088.
2. Derived from NHANES III, unpublished data, provided by the Centers for Disease Control, National Center for Health Statistics, as reported in *The Fifth Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure.*

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.

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