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$_2$-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

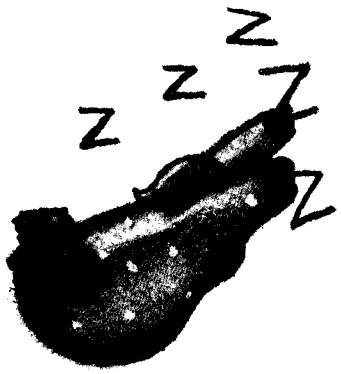
8728-3R

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

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

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

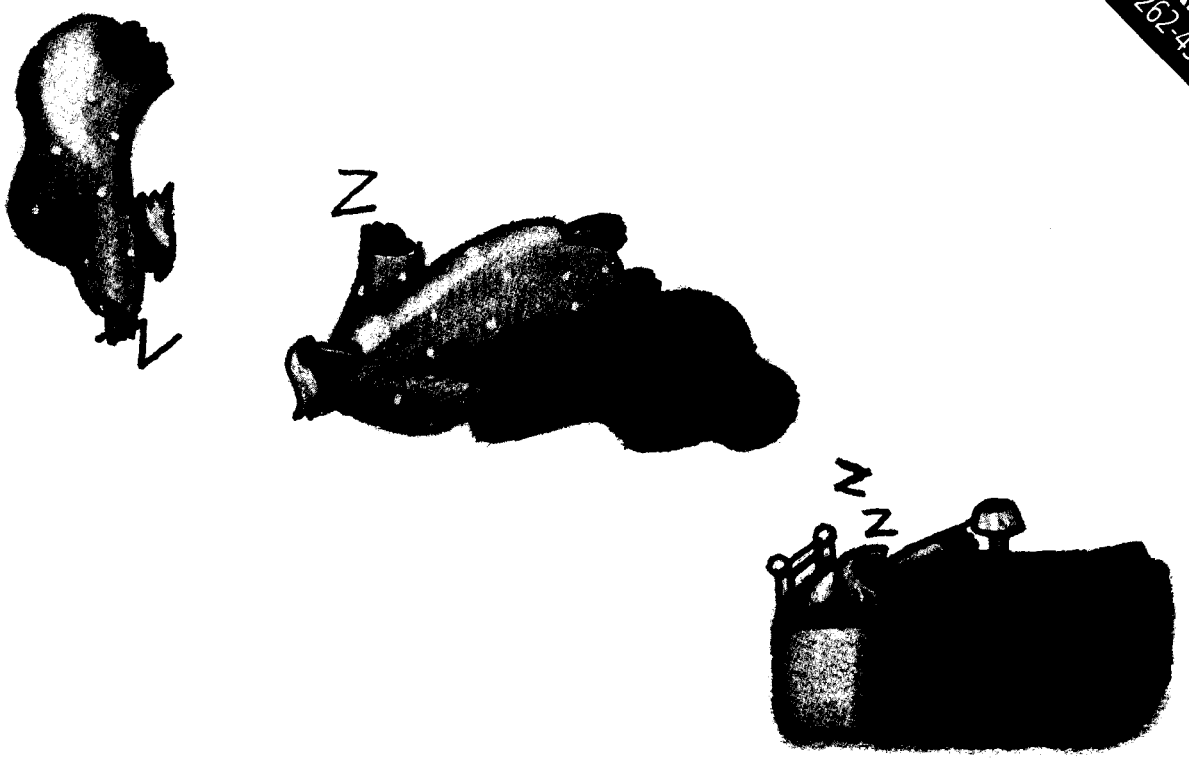
- A short half-life — mean 2.5 hours, with no active metabolites
- No evidence of significant daytime sedation or psychomotor impairment[1,2,5,6]

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.

Indicated For Short-Term Management of Insomnia

- 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.

Recommended Dosage:

For normal 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.

- In patients with hepatic dysfunction, dosage should be reduced and appropriate monitoring instituted.

The First in a New Chemical Class of Sleep Agents

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

Ambien™ (zolpidem tartrate)

BRIEF SUMMARY

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

None known.

WARNINGS

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

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

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

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

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

PRECAUTIONS

General

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

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

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

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

Laboratory tests: There are no specific laboratory tests recommended.

Drug Interactions

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

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

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

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

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

Carcinogenesis, mutagenesis, impairment of fertility

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

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

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

Pregnancy

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

Teratology studies were conducted in rats and rabbits.

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

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

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

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

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

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

The use of Ambien in nursing mothers is not recommended.

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

ADVERSE REACTIONS

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

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

Incidence in controlled clinical trials

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DRUG ABUSE AND DEPENDENCE

Controlled substance: Schedule IV.

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

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

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

OVERDOSAGE

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

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

The possibility of multiple drug ingestion should be considered.

Caution: Federal law prohibits dispensing without prescription.

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References: 1. Data on file, Searle. 2. Merlotti L, Roehrs T, Koshorek G, et al. The dose effects of zolpidem on the sleep of healthy normals. *J Clin Psychopharmacol.* 1989;9:9-14. 3. Vogel GW, Scharf M, Walsh J, et al. Effects of chronically administered zolpidem on the sleep of health insomniacs. *Sleep Research.* 1989;18:80. Abstract. 4. Scharf MB, Mayleben DW, Kaffeman M, et al. Dose response effects of zolpidem in normal geriatric subjects. *J Clin Psychiatry.* 1991;52:77-83. 5. Walsh JK, Schweitzer PK, Sugerman JL, et al. Transient insomnia associated with a 3-hour phase advance of sleep time and treatment with zolpidem. *J Clin Psychopharmacol.* 1990;10:184-189. 6. Oswald I, Adam K. A new look at short-acting hypnotics. In: Sauvanet JP, Langer SZ, Morselli PL, eds. *Imidazopyridines in Sleep Disorders.* New York, NY: Raven Press; 1988:253-259.

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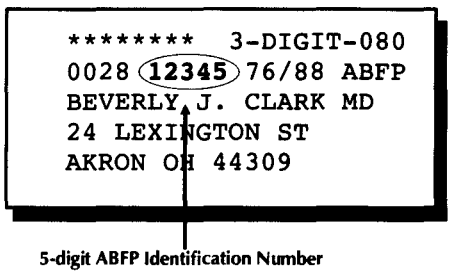

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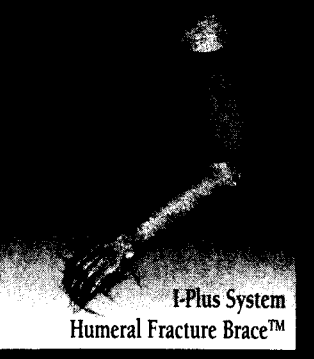

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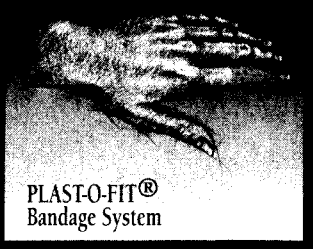

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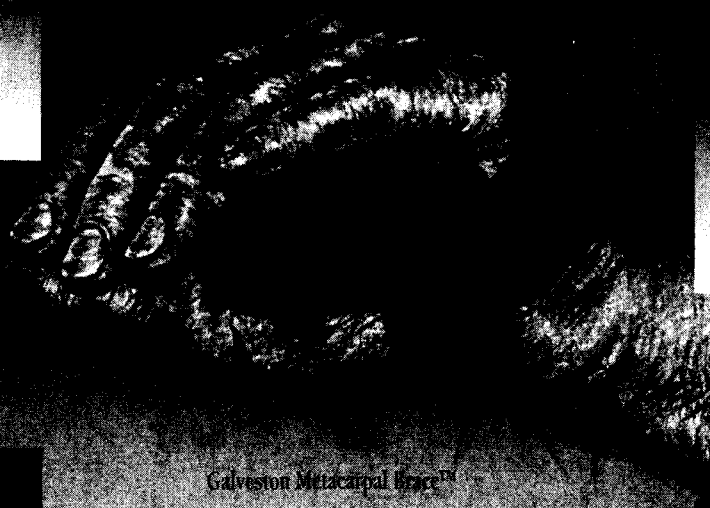

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2. McCarthy GM, McCarty DJ. Effect of topical capsaicin in the therapy of painful osteoarthritis of the hands. *J Rheumatol.* 1992;19:604–607.
3. Lotz M, Weisman M, Yaksh T, Hagaman C, Flynn P. Effects of topical capsaicin (0.075%) on substance P and prostaglandin E_2 in synovial fluid: a double-blind study. *Arthritis Rheum.* 1992;35(9):S235.

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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.

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 = 56
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.

AVM GROUP
of MERCK & CO., INC.

For more detailed information, consult your Astra/Merck Specialist or see complete Prescribing Information.
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7650203 3000-0476/93/12-09/Ppl

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*Based on patient weight of 50 kg