What's missing?

Perhaps it's PLENDIL.

Because of the greater rate of severe hypertension in blacks, more black patients will require multidrug therapy.[1] What's more, non-insulin-dependent diabetes is twice as prevalent in black patients as compared to white patients.[1]

Often, PLENDIL is appropriate. In clinical trials, blood pressure response was similar in black and non-black patients.* And, PLENDIL may be used for many hypertensive patients with or without concomitant disorders, such as: hypercholesterolemia, diabetes, impaired renal function, COPD, or asthma.

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

PLENDIL. A highly effective calcium channel blocker for hypertension.

Alone or in combination with another antihypertensive agent.

Plendil®

(felodipine) Tablets, 5 mg, 10 mg

Because you consider the whole patient.

* Data available upon request from Medical Affairs, Astra/Merck Group of Merck & Co., Inc., 725 Chesterbrook Boulevard, Wayne, PA 19087. Please request information packet #DA-PLN4.

PLENDIL is contraindicated in patients who are hypersensitive to this product. Please see brief summary of Prescribing Information on page following next page.

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


FRAZIER

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.

BRIEF SUMMARY

TABLETS

PLENDIL®

(FELODIPINE)

EXTENDED-RELEASE TABLETS

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

PRECAUTIONS

General

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

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

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

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

Information for Patients

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

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

Drug Interactions

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

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

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

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

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

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

Pregnancy

Pregnancy Category C

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

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

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

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

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

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

Clinical Laboratory Test Findings

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

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

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

OVERDOSAGE

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

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

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

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

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

DOSAGE AND ADMINISTRATION

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

PLENDIL should be swallowed whole and not crushed or chewed.

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

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

For more detailed information, consult your Astra/Merck Specialist or see complete Prescribing Information.
Astra/Merck Group of Merck & Co., Inc.
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*Registered trademark of AB Astra
†Based on patient weight of 50 kg

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TAKE EFFECTIVE CONTROL OF BED-WETTING

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

Nighttime fluid intake should be restricted to decrease the potential occurrence of fluid overload; serum electrolytes should be checked at least once when therapy is continued beyond 7 days.

DDAVP® Nasal Spray
(desmopressin acetate) 5mL

DRY NIGHTS FOR GOOD MORNINGS

Please see brief summary of prescribing information on adjacent page.

ARCHIVES OF FAMILY MEDICINE

VOL 3 NO. 6, JUNE 1994

American Medical Association
Physicians dedicated to the health of America

A Little Means A Lot To The Older Hypertensive

Comparable antihypertensive efficacy to 2.5 mg[1] with the safety profile of a lower once-daily dose*

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

Safe and effective for step-down therapy

Side-effect profile compatible with other antihypertensive agents

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

LOW-DOSE ONCE-DAILY

LOZOL® 1.25 MG

INDAPAMIDE TABLETS

* *In patients with mild or moderate hypertension, a 4-week, single-blind placebo washout period was followed by an 8-week, open-label treatment period with LOZOL 2.5 mg. Patients responding to LOZOL 2.5 mg entered an 8-week, double-blind, randomized treatment period with either LOZOL 2.5 mg or LOZOL 1.25 mg. Treatment success was defined as a decrease in supine diastolic blood pressure to 90 mm Hg or less by week 8 of the double-blind period.*

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

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

As in all step-down therapy, the patient should be monitored for maintenance of blood pressure control.

Please see brief summary of prescribing information below.

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

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

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

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

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

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

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

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

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

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One in three adults say they occasionally have trouble sleeping.[1]

Now you can help with...

More sleep, better sleep, through the night

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

From a unique class of non-benzodiazepine sleep agents

More sleep

Total sleep time significantly increased compared with placebo. Patients fall asleep quickly; generally within 20 to 30 minutes.[2-4]

Better sleep

Awakenings were reduced, compared to placebo.

Through the night

No evidence of increased wakefulness during the last third of the night. Normal sleep stages are generally preserved[2] (clinical significance unknown).

Mean percent of time in each sleep stage[2]

In this multicenter, double-blind, randomized, controlled study of 631 healthy volunteers, no significant differences were found between the durations of sleep stages.[2]

Short half-life

Mean 2.5-hour half-life, with no active metabolites.

With no objective evidence of tolerance or rebound insomnia

In studies of up to 35 consecutive nights at recommended doses.[2,3]

Favorable safety and tolerability profile

Adverse events with dosages of ≤ 10 mg that were statistically significant vs placebo

Short-term: ≤10 nights		Long-term: 28 to 35 nights	
drowsiness	2%	dizziness	5%
dizziness	1%	drugged feelings	3%
diarrhea	1%		

Recommended dosage

For adults: one 10-mg tablet

For elderly/debilitated patients: one 5-mg tablet

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

AMBIEN is indicated for the short-term treatment of insomnia. Prescriptions should not exceed a 1-month supply. Hypnotics should generally be limited to 7 to 10 days of use. Reevaluation of the patient is recommended if they are taken for more than 2 to 3 weeks.
In patients with hepatic dysfunction, treatment should be initiated with a 5-mg dose and patients closely monitored.

AMBIEN®
(ZOLPIDEM TARTRATE) CIV
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MORE SLEEP, BETTER SLEEP, THROUGH THE NIGHT

vs placebo

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

AMBIEN®
(ZOLPIDEM TARTRATE)©
5-MG & 10-MG TABLETS

BRIEF SUMMARY

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

None known.

WARNINGS

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

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

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

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

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

PRECAUTIONS

General

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

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

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

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

Laboratory tests: There are no specific laboratory tests recommended.

Drug interactions

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

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

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

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

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

Carcinogenesis, mutagenesis, impairment of fertility

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

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

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

Pregnancy

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

Teratology studies were conducted in rats and rabbits.

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

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

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

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

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

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

The use of Ambien in nursing mothers is not recommended.

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

ADVERSE REACTIONS

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

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

Incidence in controlled clinical trials

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

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

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

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

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

Body System/ Adverse Event*	Zolpidem (≤10 mg) (N=152)	Placebo (N=161)
Autonomic Nervous System		
Dry mouth	3	1
Body as a Whole		
Allergy	4	1
Back pain	3	2
Influenza-like symptoms	2	–
Chest pain	1	–
Fatigue	1	2
Cardiovascular System		
Palpitation	2	–
Central and Peripheral Nervous System		
Headache	19	22
Drowsiness	8	5
Dizziness	5	1
Lethargy	3	1
Drugged feeling	3	–
Lightheadedness	2	1
Depression	2	1
Abnormal dreams	1	–
Amnesia	1	–
Anxiety	1	1
Nervousness	1	3
Sleep disorder	1	–
Gastrointestinal System		
Nausea	6	6
Dyspepsia	5	6
Diarrhea	3	2
Abdominal pain	2	2
Constipation	2	1
Anorexia	1	1
Vomiting	1	1
Immunologic System		
Infection	1	1
Musculoskeletal System		
Myalgia	7	7
Arthralgia	4	4

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

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

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

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

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

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

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

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

DRUG ABUSE AND DEPENDENCE

Controlled substance: Schedule IV.

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

4/11/94

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April 1994
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CARDIZEM® CD

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IN HYPERTENSION OR ANGINA

CARDIZEM® CD

(diltiazem HCl)

FOR EFFECTIVE 24-HOUR CONTROL

ONCE A DAY

CVM94021201

HEMODYNAMIC EFFECTS

In hypertension[1]

- The magnitude of blood pressure reduction is related to the degree of hypertension
- Low incidence of vasodilatory side effects
- No reflex tachycardia is associated with chronic antihypertensive effects

In angina[1]

- Potent dilator of coronary arteries* and reduces vasospasm
- Appropriate decrease in heart rate with a low incidence (<1%) of reflex tachycardia
- Little or no negative inotropic effect in patients with normal ventricular function†

WELL-TOLERATED CONTROL REGARDLESS OF AGE OR GENDER‡

- A side-effect discontinuation rate comparable to placebo in both hypertension and angina trials[2]
- Most commonly reported side effects are headache (5.4%), bradycardia (3.3%), first-degree AV block (3.3%), dizziness (3.0%), edema (2.6%), ECG abnormality (1.6%), and asthenia (1.8%)[1]

* Demonstrated in patients with vasospastic angina.
† See Warnings and Clinical Pharmacology sections in prescribing information.
‡ In clinical trials with Cardizem CD.

Please see brief summary of prescribing information on next page.

ONCE-A-DAY

CARDIZEM® CD

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

FOR HYPERTENSION OR ANGINA

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

FOR HYPERTENSION OR ANGINA

℞ *Cardizem CD Start with one 180-mg capsule daily*

Brief Summary of
Prescribing Information as of April 1993

CARDIZEM® CD
(diltiazem HCl)
Capsules

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

WARNINGS
1. **Cardiac Conduction**. CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3290 patients or 0.40%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure**. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of CARDIZEM (diltiazem hydrochloride) in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.
3. **Hypotension**. Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury**. Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS
General
CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters of renal and hepatic function should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.
Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions
Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with other agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)
As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Especially in patients with renal and/or hepatic impairment, dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, may require adjustment when starting or stopping concomitantly administered diltiazem to maintain optimum therapeutic blood levels.
Beta-blockers. Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.
Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. In vitro, propranolol appears to be displaced from its binding sites by diltiazem. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)
Cimetidine. A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1200 mg per day and a single dose of diltiazem 60 mg. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.
Digitalis. Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)
Anesthetics. The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.
Cyclosporine. A pharmacokinetic interaction between diltiazem and cyclosporine has been observed during studies involving renal and cardiac transplant patients. In renal and cardiac transplant recipients, a reduction of cyclosporine dose ranging from 15% to 48% was necessary to maintain cyclosporine trough concentrations similar to those seen prior to the addition of diltiazem. If these agents are to be administered concurrently, cyclosporine concentrations should be monitored, especially when diltiazem therapy is initiated, adjusted, or discontinued.
The effect of cyclosporine on diltiazem plasma concentrations has not been evaluated.
Carbamazepine. Concomitant administration of diltiazem with carbamazepine has been reported to result in elevated serum levels of carbamazepine (40% to 72% increase), resulting in toxicity in some cases. Patients

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

Pregnancy
Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was an increased incidence of stillbirths at doses of 20 times the human dose or greater.
There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

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

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

ADVERSE REACTIONS
Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.
The following table presents the most common adverse reactions reported in placebo-controlled angina and hypertension trials in patients receiving CARDIZEM CD up to 360 mg with rates in placebo patients shown for comparison.

CARDIZEM CD Capsule Placebo-Controlled Angina and Hypertension Trials Combined

Adverse Reactions	Cardizem CD (n=607)	Placebo (n=301)
Headache	5.4%	5.0%
Dizziness	3.0%	3.0%
Bradycardia	3.3%	1.3%
AV Block First Degree	3.3%	0.0%
Edema	2.6%	1.3%
ECG Abnormality	1.6%	2.3%
Asthenia	1.8%	1.7%

In clinical trials of CARDIZEM CD capsules, CARDIZEM tablets, and CARDIZEM SR capsules involving over 3200 patients, the most common events (ie, greater than 1%) were edema (4.6%), headache (4.6%), dizziness (3.5%), asthenia (2.6%), first-degree AV block (2.4%), bradycardia (1.7%), flushing (1.4%), nausea (1.4%), and rash (1.2%).
In addition, the following events were reported infrequently (less than 1%) in angina or hypertension trials:
Cardiovascular: Angina, arrhythmia, AV block (second- or third-degree), bundle branch block, congestive heart failure, ECG abnormalities, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles
Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor
Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeusia, dyspepsia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hepatic warnings), thirst, vomiting, weight increase
Dermatological: Petechiae, photosensitivity, pruritus, urticaria
Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties
The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, erythema multiforme, exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well-documented cases of generalized rash, characterized as leukocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and CARDIZEM therapy is yet to be established.

Prescribing Information as of April 1993

Marion Merrell Dow Inc.
Kansas City, MO 64114

ccdb0493a

References: 1. Cardizem CD prescribing information. **2.** Data on file, Marion Merrell Dow Inc.

MARION MERRELL DOW INC.
U S A
KANSAS CITY, MO 64114

CVM94021201

1122C4

Once-A-Day

Adalat® CC

nifedipine EXTENDED RELEASE TABLETS

30mg, 60mg & 90mg

Real Value for Real People with Hypertension

Real Therapeutic Value

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

Real Human Value

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

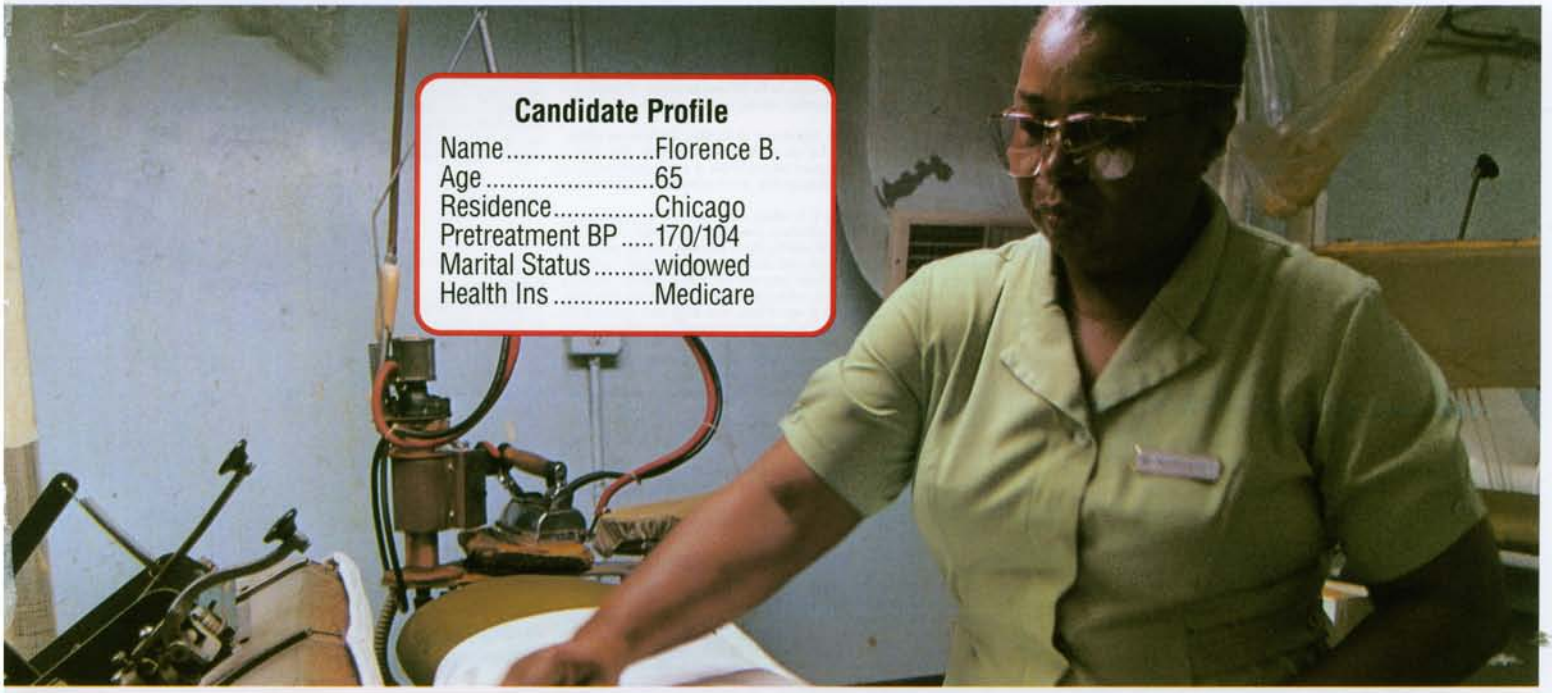
Real Economic Value

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

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

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

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



"Save up to $217† a year? That's Sunday clothes for the grandkids."

Once-A-Day

Adalat® CC
nifedipine EXTENDED RELEASE TABLETS

30mg, 60mg & 90mg

Start with*

Rx

Adalat CC 30mg once daily

Titrate, if necessary*

Rx

Adalat CC 60mg once daily

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

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

PZ100744BS 5/93

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

CONTRAINDICATIONS: Known hypersensitivity to nifedipine.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

PZ100744BS 5/93 3060
Printed in USA

References:
1. Data on file, Miles Inc.
2. *Redbook Update.* Montvale, NJ, Medical Economics Data, Inc., March 1994;p. 38.

Real People, Real Needs, Real Value

MILES

Pharmaceutical Division

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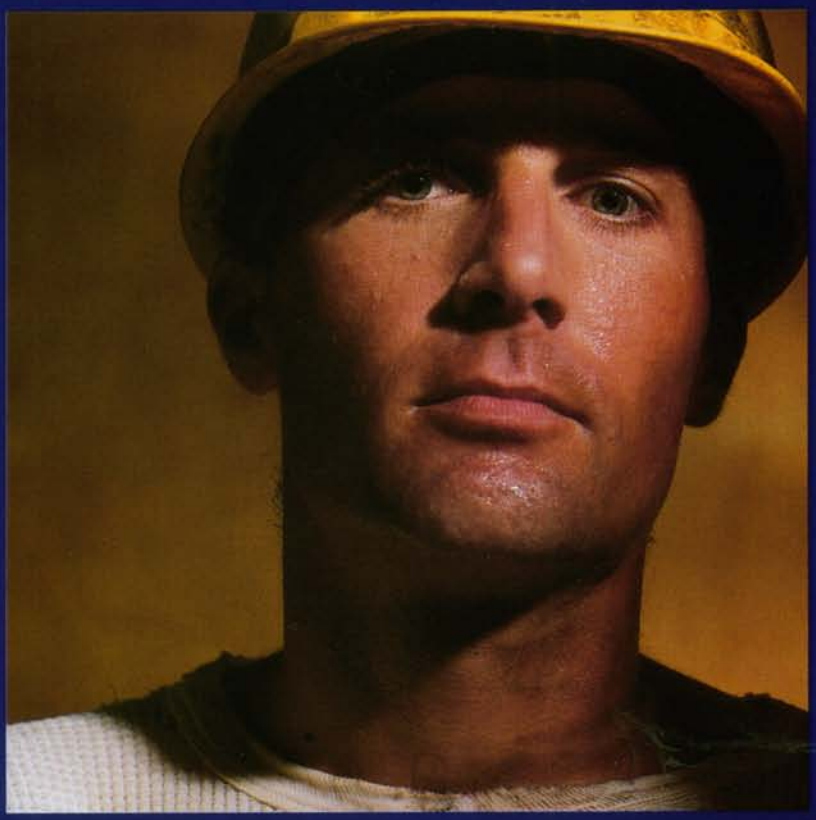
"My medicine helps,
but I still can't function fully at my job...
I've just learned to live with it."



DO YOU KNOW WHAT YOUR MIGRAINE PATIENTS THINK ABOUT THEIR CURRENT TREATMENT?

MORE OF YOUR PATIENTS MAY

Because it works fast.[1]

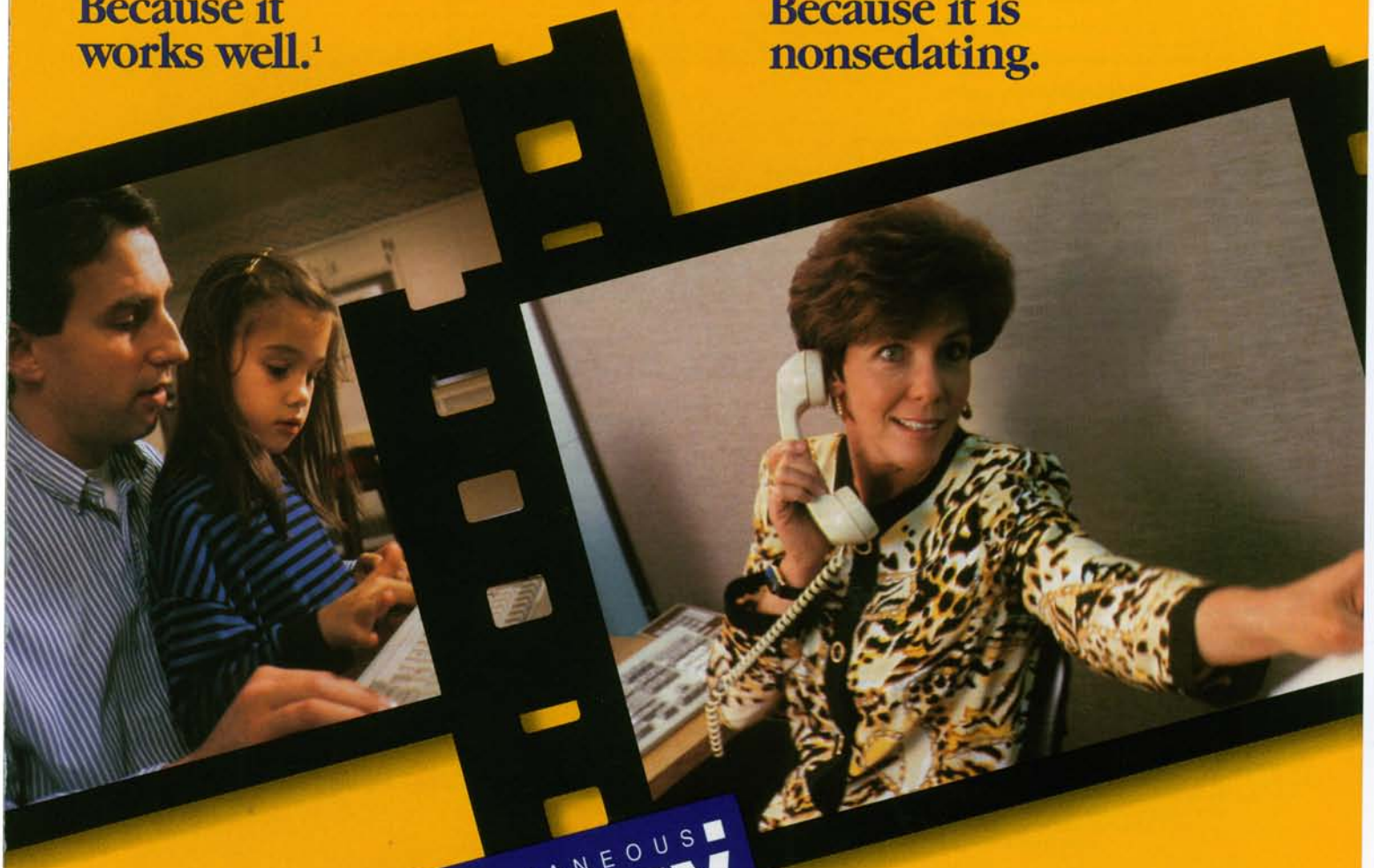
The most frequently reported adverse events associated with IMITREX are injection-site reactions (59%), atypical sensations (e.g., tingling, warm/hot sensation) (42%), and dizziness/vertigo (12%). IMITREX is contraindicated in patients with ischemic heart disease, symptoms or signs consistent with ischemic heart disease, or Prinzmetal's angina because of the potential to cause coronary vasospasm. IMITREX is contraindicated in patients with uncontrolled hypertension because it can give rise to increases in blood pressure (usually small). IMITREX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (Please see Precautions.) IMITREX should not be administered to patients with basilar or hemiplegic migraine.

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

BENEFIT FROM IMITREX

Because it works well.[1]

Because it is nonsedating.



SUBCUTANEOUS

IMITREX®

SUMATRIPTAN SUCCINATE

MIGRAINE RELIEF THAT CAN CHANGE PATIENTS' LIVES

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

BRIEF SUMMARY

Imitrex®(sumatriptan succinate) Injection

For Subcutaneous Use Only.

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

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

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

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

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

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

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

Imitrex Injection is contraindicated in patients with hypersensitivity to sumatriptan.

WARNINGS: Imitrex® Injection should not be administered to patients with basilar or hemiplegic migraine.

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

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

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

Use in Women of Childbearing Potential: (see PRECAUTIONS)

PRECAUTIONS:

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

Imitrex Injection may cause mild, transient elevation of blood pressure and peripheral vascular resistance.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Eye: Infrequent was irritation of the eye.

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

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

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

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

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

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

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

Postmarketing Experience: Frequency and causality for sumatriptan are not established for many of the following reports, which come from worldwide postmarketing experience: Episodes of Prinzmetal's angina, myocardial infarction, acute renal failure, seizure, cerebrovascular accident, dysphasia, subarachnoid hemorrhage, and arrhythmias (atrial fibrillation, ventricular fibrillation, and ventricular tachycardia). Hypersensitivity to Imitrex Injection has been reported, including anaphylactoid reactions, rash, urticaria, pruritus, erythema, and shortness of breath.

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

CERENEX™ PHARMACEUTICALS
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Calan® SR (verapamil hydrochloride)

BRIEF SUMMARY

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

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

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

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

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

Please see following page for brief summary of complete prescribing information.

SEARLE