INTRODUCING DIFLUCAN® (FLUCONAZOLE) 150 MG

† Two open-label, multicenter, randomized trials comparing a single oral Diflucan tablet (150 mg) with either 2% miconazole cream (100 mg) once nightly for 7 days or clotrimazole vaginal tablets (100 mg) once nightly for 7 days in 870 women with vaginal yeast infection due to *Candida*. Clinical cure: complete resolution of signs and symptoms present at the initial assesssment; mycologic cure: negative results from both vaginal fungal culture and KOH preparation.

‡ Results of two open, multicenter studies of single-dose Diflucan (150 mg) in 188 and 180 women, respectively, with vaginal yeast infections. Patients responding to treatment were asked to estimate times from start of therapy to onset of relief and to complete relief.

§ Wholesale acquisition cost (WAC) provided by *Medi-Span*®, July 1994. WAC may not necessarily reflect actual pharmacy or out-of-pocket costs. In studies of Diflucan, the clinical and mycologic cure rates in the fluconazole group were comparable with those of the vaginal product group (clotrimazole and miconazole). WAC includes Gyne-Lotrimin® (a registered trademark of Schering-Plough Corp); and Terazol® and Monistat® 7 (both registered trademarks of Ortho Pharmaceutical Corp).

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

THE ONLY ORAL ONE-DOSE CURE FOR MOST VAGINAL YEAST* INFECTIONS

GREAT NEWS FOR WOMEN IS HERE

Clinical and mycologic cure comparable with 7-day topicals in two separate trials—One oral Diflucan 150-mg tablet has been shown to be as effective as 7 nights of 2% miconazole cream (100 mg) or 7 nights of clotrimazole vaginal tablets (100 mg).[1†]

Early symptom relief—In two additional studies of 368 women taking Diflucan, median time to start of symptom relief was 1 day (range: 0.04 to 10 days) and 2 days (range: 0.5 to 20 days) to complete relief.[1-3‡]

Patients may require reevaluation should symptoms not improve within 3 to 5 days.

Established safety experience—More than 9 million patient days of therapy at the 150-mg dose worldwide. In US clinical trials with 870 women, the most common side effects with Diflucan were headache (13%), nausea (7%), and abdominal pain (6%).[1]

Patients respond to one-dose oral convenience

Easy to take—Diflucan can be taken anytime, anywhere, day or night, with or without food.[1]

Less expensive—Diflucan provides full-course therapy that costs less than leading prescription and most OTC products.[1§]

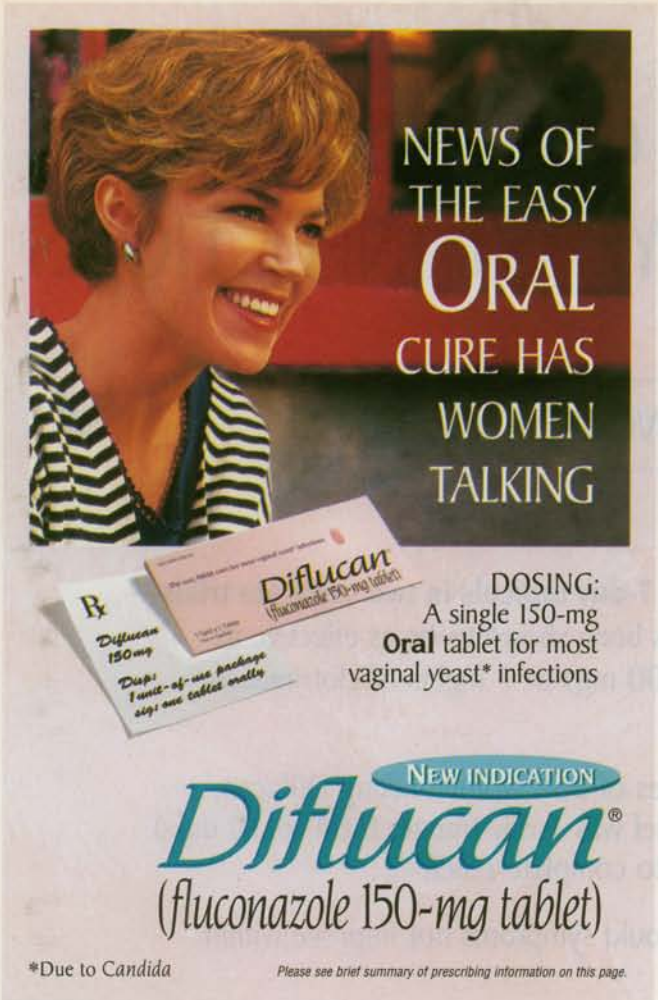
*Due to *Candida*

NEW INDICATION

Diflucan®

(fluconazole 150-mg tablet)

THE EASY **ORAL** CURE



References: **1.** Data on file. Pfizer Inc. **2.** A comparison of single-dose oral fluconazole with 3-day intravaginal clotrimazole in the treatment of vaginal candidiasis: report of an international multicentre trial. *Br J Obstet Gynecol.* 1989;96:226-232. **3.** Treatment of vaginal candidiasis with a single oral dose of fluconazole. *Eur J Clin Microbiol Infect Dis.* 1988;7:364-367.

DIFLUCAN BRIEF SUMMARY FOR VAGINAL CANDIDIASIS

INDICATION

DIFLUCAN® (fluconazole 150-mg oral tablet) is indicated for the treatment of vaginal candidiasis (vaginal yeast infections due to *Candida*).

CONTRAINDICATIONS

DIFLUCAN (fluconazole) is contraindicated in patients who have shown hypersensitivity to fluconazole or to any of its excipients. There is no information regarding cross hypersensitivity between fluconazole and other azole antifungal agents. Caution should be used in prescribing DIFLUCAN to patients with hypersensitivity to other azoles.

WARNINGS

(1) Hepatic injury: DIFLUCAN has been associated with rare cases of serious hepatic toxicity, including fatalities primarily in patients with serious underlying medical conditions. In cases of DIFLUCAN associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of the patient has been observed. Patients who develop abnormal liver function tests during DIFLUCAN therapy should be monitored for the development of more severe hepatic injury.

(2) Anaphylaxis: In rare cases, anaphylaxis has been reported.

(3) Dermatologic: Patients have rarely developed exfoliative skin disorders during treatment with DIFLUCAN. Patients who develop rashes during treatment with DIFLUCAN should be monitored closely.

PRECAUTIONS

The convenience and efficacy of the single-dose oral tablet of fluconazole regimen for the treatment of vaginal yeast infections should be weighed against the acceptability of a higher incidence of drug related adverse events with DIFLUCAN (26%) versus topical agents (16%) in U.S. comparative clinical studies (See Adverse Reactions.)

Drug Interactions

Clinically significant hypoglycemia may be precipitated by the use of DIFLUCAN with oral hypoglycemic agents; one fatality has been reported from hypoglycemia in association with combined DIFLUCAN and glyburide use. DIFLUCAN reduces the metabolism of tolbutamide, glyburide, and glipizide and increases the plasma concentration of these agents. When DIFLUCAN is used concomitantly with these or other sulfonylurea oral hypoglycemic agents, blood glucose concentrations should be carefully monitored and the dose of the sulfonylurea should be adjusted as necessary.

Prothrombin time may be increased in patients receiving concomitant DIFLUCAN and coumarin-type anticoagulants. Careful monitoring of prothrombin time in patients receiving DIFLUCAN and coumarin-type anticoagulants is recommended.

DIFLUCAN increases the plasma concentrations of phenytoin. Careful monitoring of phenytoin concentrations in patients receiving DIFLUCAN and phenytoin is recommended.

DIFLUCAN may significantly increase cyclosporine levels in renal transplant patients with or without renal impairment. Careful monitoring of cyclosporine concentrations and serum creatinine is recommended in patients receiving DIFLUCAN and cyclosporine.

Rifampin enhances the metabolism of concurrently administered DIFLUCAN. Depending on clinical circumstances, consideration should be given to increasing the dose of DIFLUCAN when it is administered with rifampin.

DIFLUCAN increased the serum concentrations of theophylline. Careful monitoring of serum theophylline concentrations in patients receiving DIFLUCAN and theophylline is recommended.

Because of the occurrence of serious cardiac dysrhythmias in patients receiving other azole antifungals in conjunction with terfenadine, an interaction study has been performed, and failed to demonstrate a clinically significant drug interaction. Although these events have not been observed in patients receiving DIFLUCAN, the co-administration of DIFLUCAN and terfenadine should be carefully monitored.

Fluconazole tablets coadministered with ethinyl estradiol- and levonorgestrel-containing oral contraceptives produced an overall mean increase in ethinyl estradiol and levonorgestrel levels: however, in some patients there were decreases up to 47% and 33% of ethinyl estradiol and levonorgestrel levels. The data presently available indicate that the decreases in some individual ethinyl estradiol and levonorgestrel AUC values with fluconazole treatment are likely the result of random variation. While there is evidence that fluconazole can inhibit the metabolism of ethinyl estradiol and levonorgestrel, there is no evidence that fluconazole is a net inducer of ethinyl estradiol or levonorgestrel metabolism. The clinical significance of these effects is presently unknown.

Physicians should be aware that interaction studies with medications other than those listed in the Clinical Pharmacology section have not been conducted, but such interactions may occur.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Fluconazole showed no evidence of carcinogenic potential in mice and rats treated orally for 24 months at doses of 2.5, 5 or 10 mg/kg/day (approximately 2-7x the recommended human dose). Male rats treated with 5 and 10 mg/kg/day had an increased incidence of hepatocellular adenomas.

Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in 4 strains of *S. typhimurium*, and in the mouse lymphoma L5178Y system. Cytogenetic studies *in vivo* (murine bone marrow cells, following oral administration of fluconazole) and *in vitro* (human lymphocytes exposed to fluconazole at 1000 µg/mL) showed no evidence of chromosomal mutations.

Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10 or 20 mg/kg or with parenteral doses of 5, 25 or 75 mg/kg, although the onset of parturition was slightly delayed at 20 mg/kg p.o. In an intravenous perinatal study in rats at 5, 20 and 40 mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg (approximately 5-15x the recommended human dose) and 40 mg/kg, but not at 5 mg/kg. The disturbances in parturition were reflected by a slight increase in the number of still-born pups and decrease of neonatal survival at these dose levels. The effects on parturition in rats are consistent with the species specific estrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole.

Pregnancy

Teratogenic Effects. Pregnancy Category C: Fluconazole was administered orally to pregnant rabbits during organogenesis in two studies, at 5, 10 and 20 mg/kg, and at 5, 25, and 75 mg/kg respectively. Maternal weight gain was impaired at all dose levels, and abortions occurred at 75 mg/kg (approximately 20-60x the recommended human dose); no adverse fetal effects were detected. In several studies in which pregnant rats were treated orally with fluconazole during organogenesis, maternal weight gain was impaired and placental weights were increased at 25 mg/kg. There were no fetal effects at 5 or 10 mg/kg; increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg (approximately 20-60x the recommended human dose) to 320 mg/kg embryolethality in rats was increased and fetal abnormalities included wavy ribs, cleft palate and abnormal cranio-facial ossification. These effects are consistent with the inhibition of estrogen synthesis in rats and may be a result of known effects of lowered estrogen on pregnancy, organogenesis and parturition.

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

Nursing Mothers

Fluconazole is secreted in human milk at concentrations similar to plasma. Therefore, the use of DIFLUCAN in nursing mothers is not recommended.

Pediatric Use

Efficacy of DIFLUCAN has not been established in children. A small number of patients from age 3 to 13 years have been treated safely with DIFLUCAN using doses of 3-6 mg/kg daily.

The safety and effectiveness of DIFLUCAN 150 mg tablets in the treatment of vaginal candidiasis in patients under 18 years of age have not been established.

ADVERSE REACTIONS

In patients receiving a single dose for vaginal candidiasis.

During comparative clinical studies conducted in the United States, 448 patients with vaginal candidiasis were treated with DIFLUCAN, 150 mg single dose. The overall incidence of side effects possibly related to DIFLUCAN was 26%. In 422 patients receiving active comparative agents, the incidence was 16%. The most common treatment-related adverse events reported in the patients who received 150 mg single dose fluconazole for vaginitis were headache (13%), nausea (7%) and abdominal pain (6%). Other side effects reported with an incidence equal to or greater than 1% included diarrhea (3%), dyspepsia (1%), dizziness (1%), and taste perversion (1%). Most of the reported side effects were mild to moderate in severity. Rarely, angioedema and anaphylactic reaction have been reported in marketing experience.

Pfizer U.S. Pharmaceuticals Group

VC105A94 Issued July 1994

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- Significant improvement in number of dry nights shown in controlled studies[1,2]
- Rapid response–substantial effect seen in as few as 1 to 3 nights of treatment[3]
- A combined 15-year record of successful and safe use in the U.S. and Europe[4]

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.

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VOL 3 NO. 10, OCTOBER 1994

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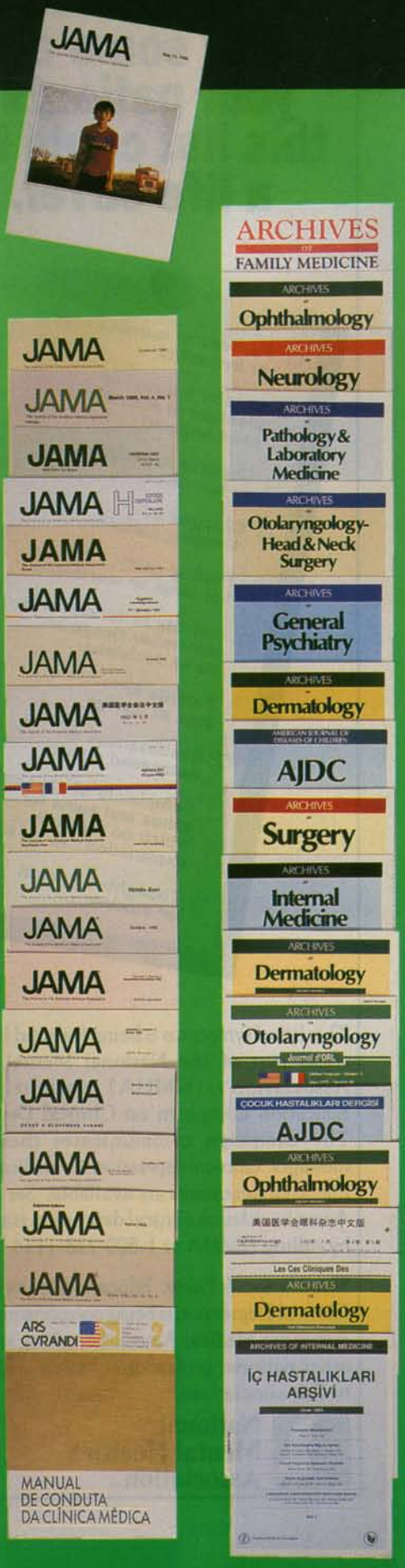

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THE COUGH LIQUIDATOR

Cough relief designed to make remaining coughs more productive.
Now, help relieve dry, hacking coughs and make the most of remaining coughs with new Brontex—the codeine formula with the most guaifenesin.

3 times more guaifenesin per tablet than a teaspoon of other codeine brands.*
Only new Brontex combines 10 mg codeine—the most commonly prescribed level of the antitussive many doctors prefer—with 300 mg guaifenesin—the expectorant with the time-proven safety profile—in a convenient, single-tablet dose.

Only Brontex exceeds the minimum therapeutic requirements for guaifenesin.
Unlike other codeine brands, new Brontex, with its convenient dosing regimen, reaches well into the daily therapeutic range for guaifenesin (1,200 mg to 2,400 mg) set by federal guidelines.

Now for dry, unproductive coughs, there's new Brontex—the codeine cough formula with the most guaifenesin.

FROM THE MAKERS OF ENTEX® PRODUCTS

NEW **Brontex®** (III)

CODEINE PHOSPHATE...10mg
(Warning: May be habit forming)
GUAIFENESIN.....300mg

FEWER COUGHS, WETTER COUGHS

Please see brief summary of prescribing information on next page.

FROM THE MAKERS OF ENTEX® PRODUCTS

NEW Brontex® III

CODEINE PHOSPHATE...10mg
(Warning: May be habit forming)
GUAIFENESIN.....300mg

Cough relief designed to make remaining coughs more productive

Up to 3 times more guaifenesin than other codeine brands

Exceeds the minimum therapeutic requirements for guaifenesin set by federal guidelines

FEWER COUGHS, WETTER COUGHS

Codeine may cause sedation and have additive sedative effects with other CNS depressants.

* Recommended dosing for most codeine/guaifenesin products is two teaspoons every four hours.

Brontex®

(codeine phosphate/guaifenesin) tablets

DESCRIPTION: Each **Brontex®** tablet and 4 teaspoonfuls (20 mL) of **Brontex** liquid contains
codeine phosphate.....10 mg
Warning — May be habit forming
guaifenesin.....300 mg

INDICATIONS AND USAGE: Temporarily relieves cough due to minor throat and bronchial irritation as may occur with a cold, or inhaled irritants. Helps loosen phlegm (mucus) and thin bronchial secretions to rid the bronchial passageways of bothersome mucus.

CONTRAINDICATIONS: Brontex tablets are contraindicated in patients with known hypersensitivity to any of its ingredients. **Brontex** tablets are contraindicated for use in patients with asthma.

WARNINGS: Codeine is not recommended for use in children under 2 years of age. Children under 2 years may be more susceptible to the respiratory depressant effects of codeine, including respiratory arrest, coma, and death.

PRECAUTIONS: General: Codeine should be used with extreme caution in patients with severe CNS depression, respiratory depression, or those prone to respiratory depression, acute alcoholism, chronic pulmonary disease and those with substantially decreased respiratory reserve. Codeine should be administered with caution in patients with acute abdominal conditions, convulsive disorders, significant hepatic or renal impairment, fever, hypothyroidism, Addison's disease, ulcerative colitis, prostatic hypertrophy, in patients with recent gastrointestinal or urinary tract surgery, and in the very young or elderly or debilitated patients.

Administration of codeine may be accompanied by histamine release and should be used with caution in children with atopy.

Dosage of codeine should not be increased if cough fails to respond; an unresponsive cough should be reevaluated in 5 days or sooner for possible underlying pathology, such as foreign body or lower respiratory tract disease.

Codeine may cause or aggravate constipation.

Hypotensive Effects: Codeine may produce hypotension in ambulatory patients.

Head Injury and Increased Intracranial Pressure: The risk of respiratory depression and elevation of cerebrospinal fluid pressure is increased by opiate agonists, including codeine, in the presence of head injury, intracranial lesions, or a pre-existing increase in intracranial pressure. They also may produce adverse reactions such as sedation and pupillary changes which may obscure the clinical course of patients with head injuries.

Respiratory Conditions with Productive Cough or Chronic Respiratory Disease: The risks and benefits of opiate agonists or cough suppressants, including codeine, should be carefully considered in illness associated with productive cough or in chronic respiratory disease where interference with ability to clear the tracheobronchial tree of secretions would have a deleterious effect on the patient's respiratory function.

Information for Patients: Brontex tablets may cause marked drowsiness or may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. Ambulatory patients should be told to avoid engaging in such activities until it is known that they do not become drowsy or dizzy from **Brontex** tablets. Children should be supervised to avoid potential harm in bike riding or in other hazardous activities.

The concomitant use of alcohol or other central nervous system depressants, including opiate agonists, sedatives, hypnotics, and tranquilizers, may have an additive effect and should be avoided or their dosage reduced.

Codeine, like other opiate agonists, may produce orthostatic hypotension in some ambulatory patients. Patients should be cautioned accordingly.

Drug Interactions: Caution should be used when taking this product with CNS depressants including alcohol, sedatives, tranquilizers and drugs used for depression, especially monoamine oxidase inhibitors (MAOIs). These combinations may cause greater sedation than is caused by the products used alone.

Drug/Laboratory Test Interactions: Guaifenesin has been reported to interfere with clinical laboratory determinations of urinary 5-hydroxyindoleacetic acid (5-HIAA) and urinary vanillylmandelic acid (VMA).

Because opiate agonists may increase biliary tract pressure, with resultant increases in plasma amylase or lipase levels, determination of these enzyme levels may be unreliable for 24 hours after an opiate agonist has been given.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies with **Brontex** tablets in animals to evaluate carcinogenic, mutagenic, or impairment of fertility potential have not been conducted. Studies conducted by the National Toxicology Program with codeine in rats and mice to evaluate its carcinogenic potential are in progress.

Pregnancy:

Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with **Brontex** tablets. It is also not known whether **Brontex** tablets can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. **Brontex** tablets should be given to a pregnant woman only if clearly needed.

Studies with codeine in hamsters and mice to evaluate its developmental toxicity potential have been reported by the National Toxicology Program. Codeine produced a decrease in mean fetal weight in both hamsters and mice, but did not produce structural malformations.

Nonteratogenic Effects: Dependence has been reported in newborns whose mothers took opiates regularly during pregnancy. Signs of withdrawal include irritability, excessive crying, tremors, hyperreflexia, fever, vomiting, and diarrhea. These

Brontex® (codeine phosphate/guaifenesin) tablets

signs usually disappear during the first few days of life.

Labor and Delivery: Use should be avoided during labor and delivery. Opiates cross the placental barrier. The closer to delivery and the larger the dose used, the greater the possibility of respiratory depression in the newborn. If the mother received opiates during labor, the newborn should be closely observed for signs of respiratory depression. Resuscitation, and in severe cases, naloxone may be required. Codeine may also prolong labor.

Nursing Mothers: Codeine is excreted in breast milk in amounts that are probably insignificant when given at usual therapeutic dose. It is not known whether guaifenesin is excreted in breast milk. Caution should be exercised when **Brontex** tablets are administered to a nursing mother. The possibility of clinically important amounts of codeine being excreted in breast milk in individuals abusing codeine should be considered.

Pediatric Use: Brontex tablets are not recommended for use in children below the age of 12 years. **Brontex** liquid is not recommended for use in children below the age of 6 years.

ADVERSE REACTIONS:

Nervous System: CNS depression, particularly respiratory depression, light-headedness, dizziness, sedation, euphoria, dysphoria, headache, transient hallucination, disorientation, visual disturbances, and convulsions.

Cardiovascular: Tachycardia, bradycardia, palpitation, faintness, syncope, orthostatic hypotension (common to opiate agonists), and circulatory depression.

Gastrointestinal: Nausea, vomiting, stomach pain, constipation, and biliary tract spasm. Patients with chronic ulcerative colitis may experience increased colonic motility; in patients with acute ulcerative colitis, toxic dilation has been reported.

Genitourinary: Oliguria and urinary retention; antidiuretic effect has been reported (common to opiate agonists).

Allergic: Infrequent pruritus, urticaria, angioneurotic edema, laryngeal edema, and rare anaphylactic reaction.

Other: Flushing of the face, sweating, and weakness.

DRUG ABUSE AND DEPENDENCE: Brontex tablets are a Schedule III Controlled Substance. **Brontex** liquid is a Schedule V controlled substance.

Codeine is known to be subject to abuse; however, the abuse potential of oral codeine is lower than that of most other opiate agonists because of its lower potency at therapeutic doses. However, codeine must be administered only under close supervision to patients with a history of drug abuse or dependence.

Psychological dependence, physical dependence, and tolerance are known to occur with codeine.

OVERDOSAGE:

Signs and Symptoms: Serious overdose with codeine is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, miosis (mydriasis may occur in terminal necrosis or hypoxia), skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Treatment: The treatment of overdosage should provide symptomatic and supportive care. Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation as necessary. The narcotic antagonist naloxone is a specific antidote against respiratory depression resulting from overdosage or unusual sensitivity to opiate agonists, including codeine. Therefore, an appropriate dose of naloxone hydrochloride (see package insert) may be administered, preferably by the intravenous route, and simultaneously with efforts at respiratory resuscitation. Since the duration of action of codeine may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

If the amount ingested is considered dangerous or excessive, induce vomiting with ipecac syrup unless the patient is convulsing, comatose, or has lost the gag reflex, in which case perform gastric lavage using a large-bore tube. If indicated, follow with activated charcoal and a saline cathartic.

DOSAGE AND ADMINISTRATION:

Adults and children 12 years of age and older: one tablet every 4 hours.

Brontex tablets are not recommended for children under 12 years of age.

Liquid: Adults and children 12 years of age and older: 4 teaspoonfuls every 4 hours. **Children 6 to under 12 years of age:** 2 teaspoonfuls every 4 hours.

HOW SUPPLIED:

Brontex tablets are available as a red, capsule-shaped tablet, embossed **"BRONTEX".**

NDC 0149-0440-01 bottle of 100.

Brontex liquid is available as **NDC** 0149-0441-16 1 pint (473 mL) bottle.

Store at controlled room temperature (59°-86°F or 15°-30°C).

CAUTION: Federal law prohibits dispensing without prescription.

Procter & Gamble Pharmaceuticals
Cincinnati, Ohio 45202

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Patent Pending

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

* *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.

LOW-DOSE ONCE-DAILY

LOZOL® 1.25 MG

INDAPAMIDE TABLETS

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

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

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

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

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

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

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

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

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

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receiving methylphenidate and in four (11%) while receiving placebo, a highly significant difference statistically and clinically." In contrast, Mattes et al[11] concluded that:

No overall benefit from methylphenidate was evident, regardless of childhood history of ADD-H [attention-deficit disorder with hyperactivity]. Approximately 25% of the sample appeared clinically to benefit from methylphenidate. . . . Even among the responders, benefit was generally not as marked nor as clinically valuable as in childhood ADD-H.

We need to define the prognosis of ADHD as seen in primary care and the spectrum of adverse outcomes in a way that is generalizable to primary care practice. Further controlled clinical trials are needed to define the appropriate pharmacological and psychological treatment of ADHD in adults, as well as in children, and to identify which treatments in children with ADHD lead to improved outcomes in adulthood.

Daniel C. Vinson, MD, MSPH
University of Missouri
Columbia

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ONCE-A-DAY

CARDIZEM® CD

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

IN HYPERTENSION OR ANGINA

CVM94021201

1122C4

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

1122C4

ONCE-A-DAY CARDIZEM® CD

(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 receiving these drugs concurrently should be monitored for a potential drug interaction.

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.
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KANSAS CITY, MO 64114

CVM94021201

1122C4

Just how powerful is it?

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

PLENDIL provides a gradual onset of action for continuous 24-hour blood-pressure control in many patients.

And, PLENDIL is suited to a broad range of your hypertensive patients — including many with concomitant disorders, such as: hypercholesterolemia, diabetes, impaired renal function, COPD, or asthma.

PLENDIL. A highly effective calcium channel blocker for blood pressure control.

Generally well tolerated at usual doses.†

Plendil®

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

Because you consider the whole patient.

*1993 IMS NDTI Prescription Data.

†Peripheral edema, generally mild, was the most common adverse event in clinical trials.

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

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

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


FRASER

BRIEF SUMMARY

TABLETS

PLENDIL®

(FELODIPINE)

EXTENDED-RELEASE TABLETS

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

PRECAUTIONS

General

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

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

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

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

Information for Patients

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

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

Drug Interactions

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

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

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

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

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

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

Pregnancy

Pregnancy Category C

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

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

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

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

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

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

Clinical Laboratory Test Findings

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

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

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

OVERDOSAGE

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

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

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

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

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

DOSAGE AND ADMINISTRATION

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

PLENDIL should be swallowed whole and not crushed or chewed.

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

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

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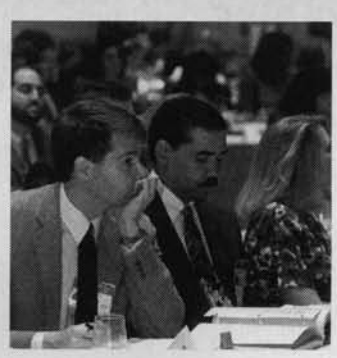

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This year's Interim Meeting in Honolulu, Hawaii, will feature an educational session titled "Physicians as Teachers: Passing The Torch." Our keynote speaker will be S. Y. Tan, MD, Director of Medical Education, St. Francis Medical Center, Honolulu, Hawaii. The program will examine the role of residents teaching residents and medical students and ways of improving teaching skills. The session begins at 11:30 noon, Friday, December 2, 1994.

For more information about the AMA Interim Meeting or joining the AMA-RPS, contact the AMA Department of Resident Physicians Services at 312/464-4751.

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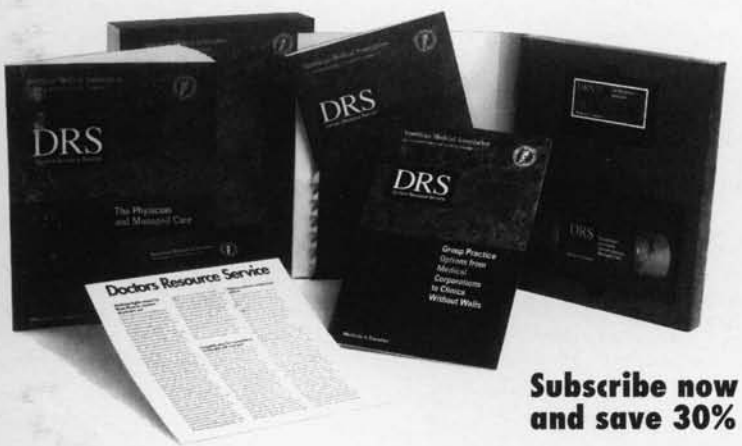

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BRIEF SUMMARY

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

SEARLE