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§]

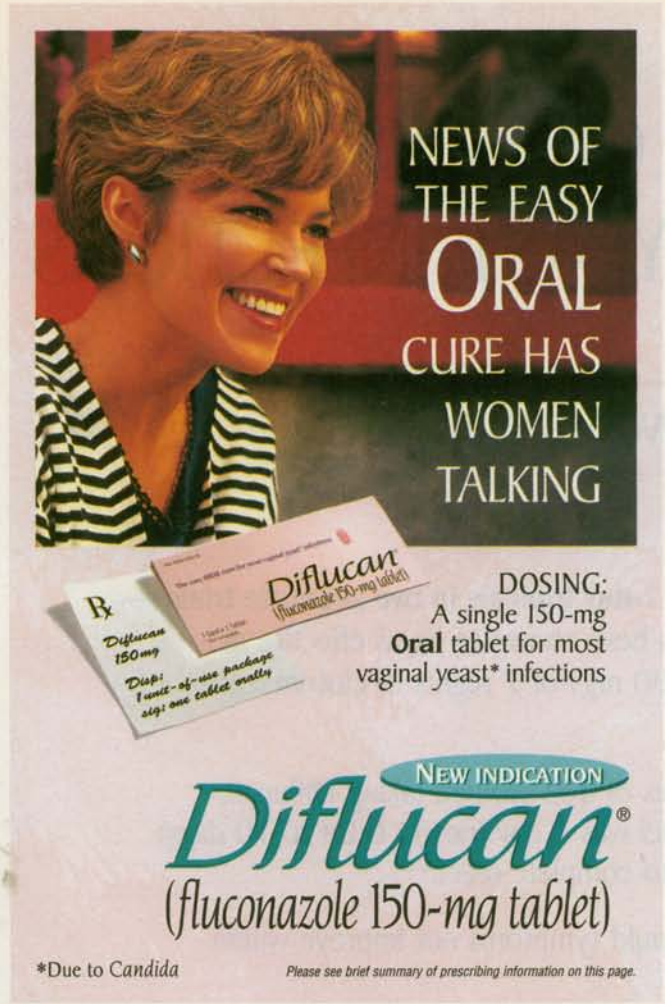
*Due to *Candida*

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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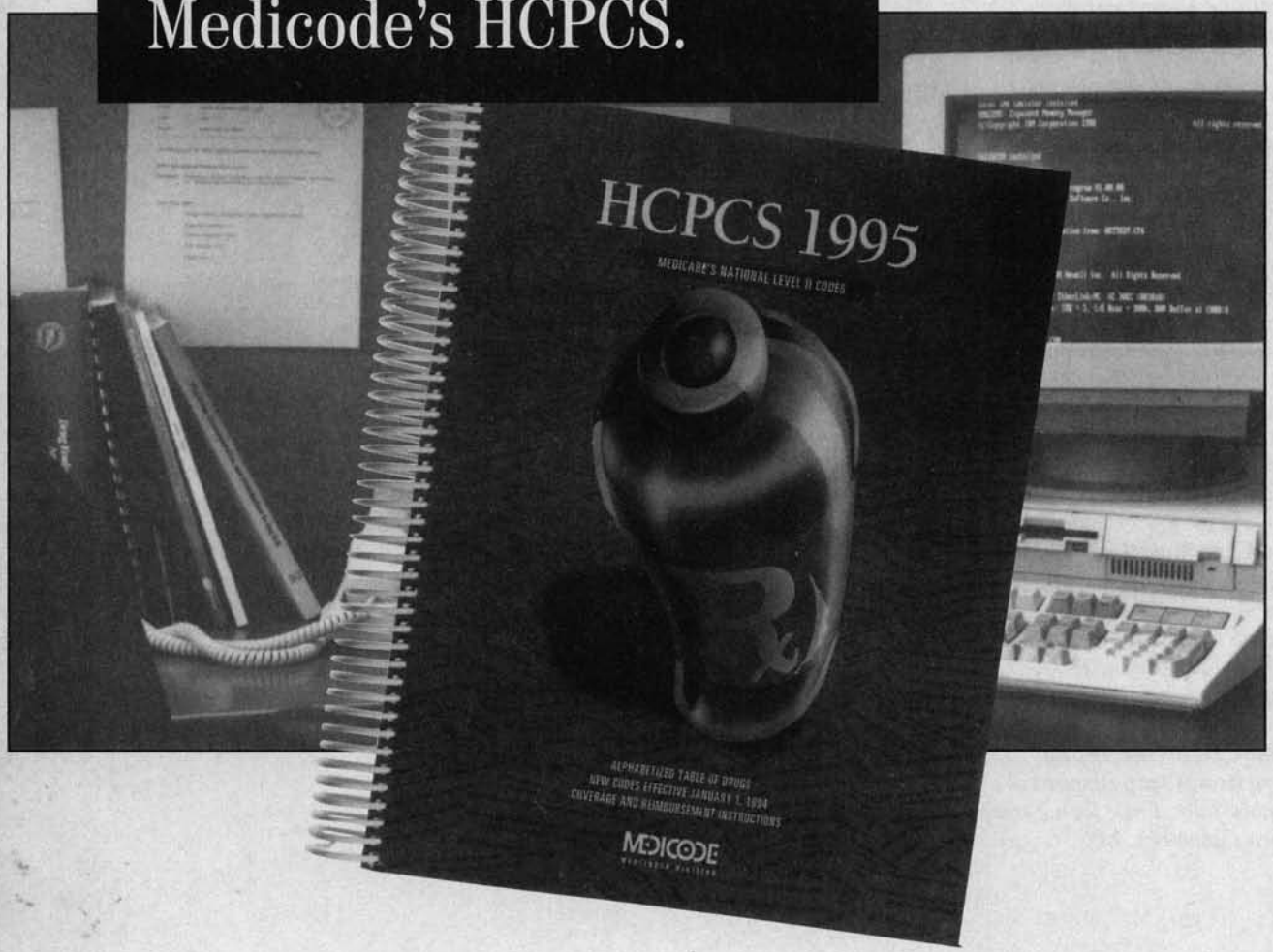

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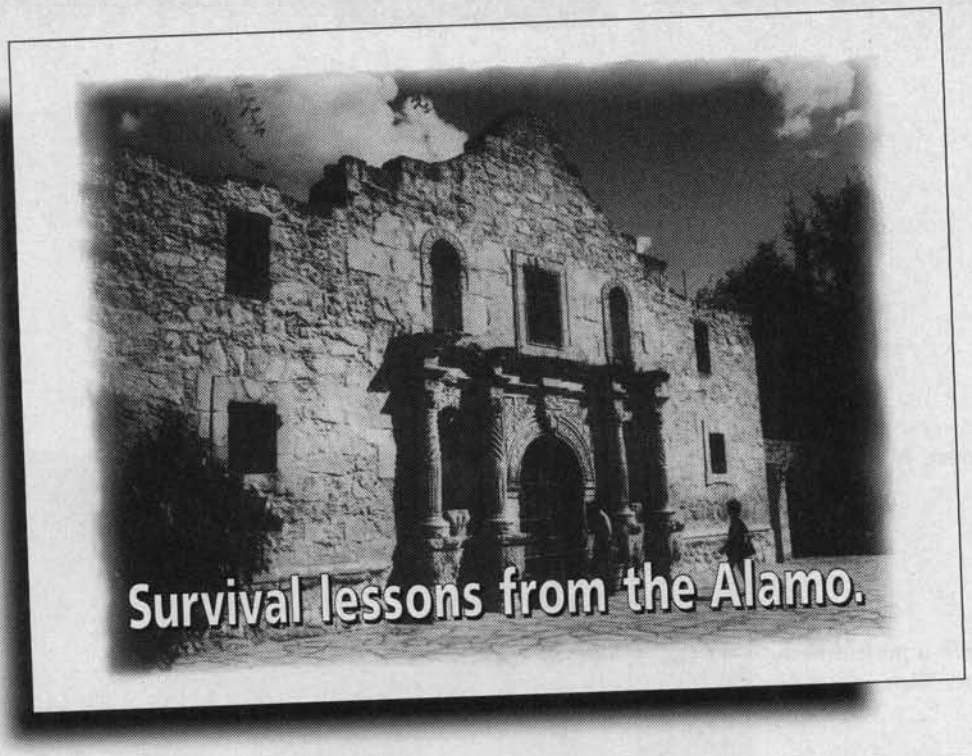

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- Regulatory constraints

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Who should attend.

The curriculum is designed to benefit experienced and newly elected or appointed medical staff leaders, including: chiefs of staff, department chairs, vice presidents of medical affairs, medical staff committee chairs, and medical staff services professionals.* Bring a team from your hospital!

For more information or to register, call **800 621-8335.**

* The AMA designates the *Interactions* conference for 18 credit hours of Category 1 of the Physician's Recognition Award of the AMA.

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For some of your patients, this list could be a life saver.

- ❑ Feelings of sadness or irritability
- ❑ Loss of interest or pleasure in activities once enjoyed
- ❑ Changes in weight or appetite
- ❑ Changes in sleeping pattern
- ❑ Feeling guilty, hopeless or worthless
- ❑ Inability to concentrate, remember things or make decisions
- ❑ Fatigue or loss of energy
- ❑ Restlessness or decreased activity
- ❑ Complaints of physical aches and pains for which no medical explanation can be found
- ❑ Thoughts of death or suicide

This list of symptoms is being featured in a print ad as part of the National Mental Health Association's (NMHA) National Public Education Campaign on Clinical Depression. The campaign communicates these basic messages: Clinical depression is a medical illness. Effective treatments are available. *See a doctor*. A free booklet on clinical depression is available by calling NMHA at 1-800-228-1114.

The National Public Education Campaign on Clinical Depression is being co-sponsored by the American Medical Association along with nine other national professional health and mental health associations.

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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 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.
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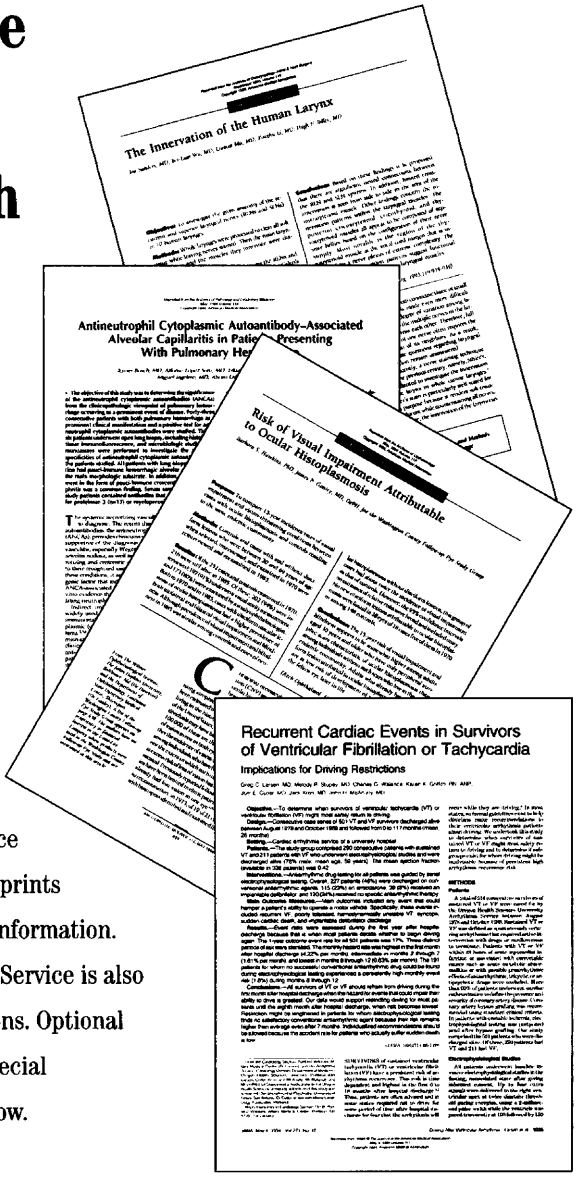

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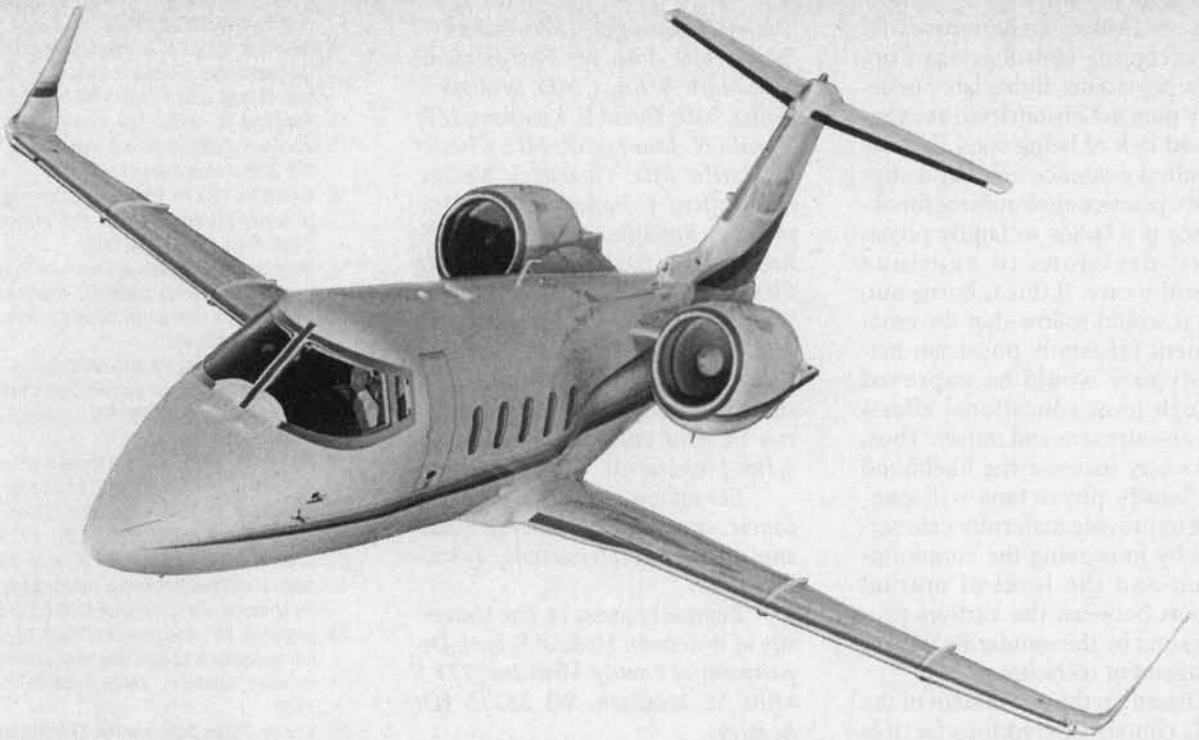

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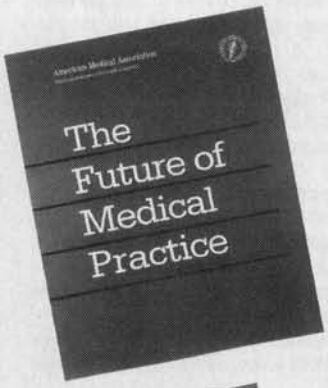

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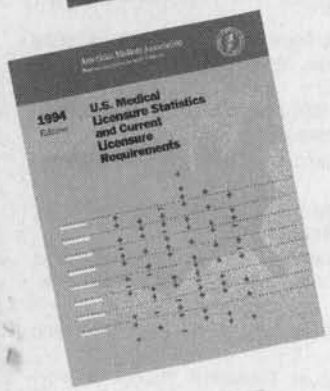

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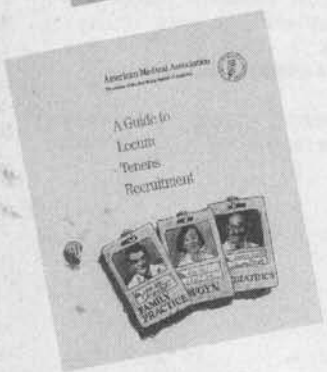

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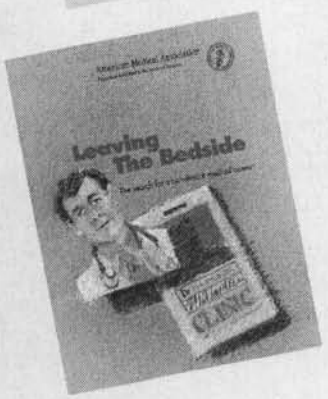

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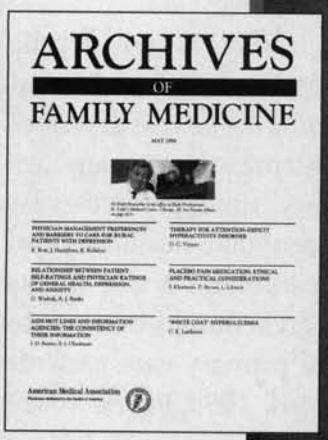

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Brief Summary

VERELAN® (Verapamil HCl)
Sustained-Release Pellet Filled Capsules

For complete Prescribing Information, consult package insert.

CLINICAL PHARMACOLOGY

Atrioventricular block can occur in patients without preexisting conduction defects (see **WARNINGS**). Acceleration of ventricular rate and/or ventricular fibrillation has been reported in patients with atrial flutter or atrial fibrillation and a coexisting accessory AV pathway following administration of verapamil (see **WARNINGS**). Food does not affect the extent or rate of the absorption of verapamil from the controlled release VERELAN capsule. The bioequivalence of VERELAN 240 mg, administered as the pellets sprinkled on applesauce and as the intact capsule, has been demonstrated. In patients with hepatic insufficiency, metabolism is delayed and elimination half-life prolonged up to 14 to 16 hours (see **PRECAUTIONS**), the volume of distribution is increased, and plasma clearance reduced to about 30% of normal.

CONTRAINDICATIONS

Severe LV dysfunction (see **WARNINGS**), hypotension (systolic pressure <90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no functioning artificial ventricular pacemaker is present), second- or third-degree AV block (if no functioning artificial ventricular pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW, LGL syndromes) (see **WARNINGS**), hypersensitivity to verapamil hydrochloride.

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-adrenergic blocker. Control milder ventricular dysfunction with optimum digitalization and/or diuretics before VERELAN is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases of hepatocellular injury 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 have developed increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving IV verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. The effect of verapamil on AV conduction and the SA node may lead to asymptomatic first-degree AV block, transient bradycardia, and sometimes nodal escape rhythms. Higher degrees of AV block, however, were infrequently (0.8%) observed. Development of marked first-degree block or progression to second- or third-degree AV block requires reduction in dosage or, rarely, discontinuation of verapamil HCl and institution of appropriate therapy. Sinus bradycardia, second-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

THE CONTENTS OF THE VERELAN CAPSULE SHOULD NOT BE CRUSHED OR CHEWED. General: 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. **Drug Interactions:** When the sprinkle method of administration is prescribed, the proper technique should be explained to the patient. (See **DOSAGE AND ADMINISTRATION** in full Prescribing Information.) 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 excess bradycardia and AV block, including complete heart block. For hypertensive patients, the risk of combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. 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, the influence of verapamil on digoxin kinetics is magnified. Maintenance digitalis doses 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. Verapamil has been given concomitantly with short- and long-acting nitrates without any undesirable drug interactions. Interaction between cimetidine and chronically administered verapamil has not been studied. In healthy volunteers, clearance of verapamil was reduced or unchanged. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may markedly reduce oral verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporine. 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. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** One 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 only if clearly needed. **Labor and Delivery:** It is not known whether verapamil use during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs labor, or increases the need for forceps delivery or other obstetric intervention. Such adverse experiences have not been reported despite a long history of verapamil HCl use in Europe for treatment of cardiac side effects of beta-adrenergic agonist agents used to treat premature labor. **Nursing Mothers:** Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use. **Pediatric Use:** Safety and efficacy of verapamil in children below the age of 18 years have not been established.

ADVERSE REACTIONS

Reversible (upon discontinuation of verapamil) nonobstructive, paralytic ileus has been infrequently reported in association with the use of verapamil. In clinical trials with 285 hypertensive patients on VERELAN for more than 1 week, the following adverse reactions were reported in greater than 1.0% of patients: constipation (7.4%); headache (5.3%); dizziness (4.2%), lethargy (3.2%); dyspepsia (2.5%); rash (1.4%); ankle edema (1.4%); sleep disturbance (1.4%); myalgia (1.1%). In clinical trials of other formulations of verapamil HCl (N = 4,954), the following reactions have occurred at rates greater than 1.0%: constipation (7.3%); dizziness (3.3%); nausea (2.7%); hypotension (2.5%); edema (1.9%); headache (2.2%); rash (1.2%); CHF/pulmonary edema (1.8%); fatigue (1.7%); bradycardia (HR<50/min) (1.4%); AV block-total 1°, 2°, 3° (1.2%), 2° and 3° (0.8%); flushing (0.6%); elevated liver enzymes (see **WARNINGS**). The following reactions, reported in 1.0% or less of patients, occurred under conditions (open trials, marketing experience) where a causal relationship is uncertain. **Cardiovascular:** angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction; palpitations, purpura (vasculitis), syncope. **Digestive System:** diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia. **Hemic and Lymphatic:** ecchymosis or bruising. **Nervous System:** cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence. **Respiratory:** dyspnea. **Skin:** arthralgia and rash, exanthema, hair loss, hyperkeratosis, maculae, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme. **Special Senses:** blurred vision. **Urogenital:** gynecomastia, impotence, increased urination, spotty menstruation.

OVERDOSAGE

Treatment should be supportive. Verapamil cannot be removed by hemodialysis. Clinically significant hypotensive reactions or high degree AV block should be treated with vasopressor agents or cardiac pacing, respectively.

DOSAGE AND ADMINISTRATION

VERELAN Pellet Filled Capsules may also be administered by carefully opening the capsule and sprinkling the pellets on a spoonful of applesauce. Please see full Prescribing Information for complete dosing and precautionary information.

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Constipation, which can be easily managed in most patients, is the most frequently reported side effect of verapamil.

Please see brief summary of Prescribing Information including CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS on adjacent page.

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