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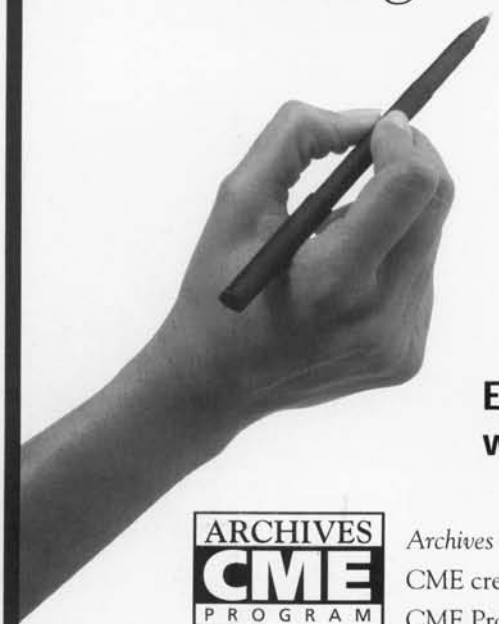

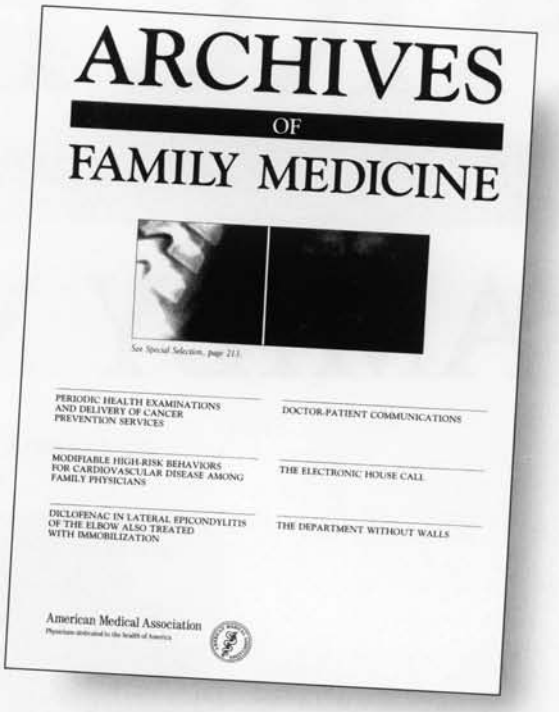

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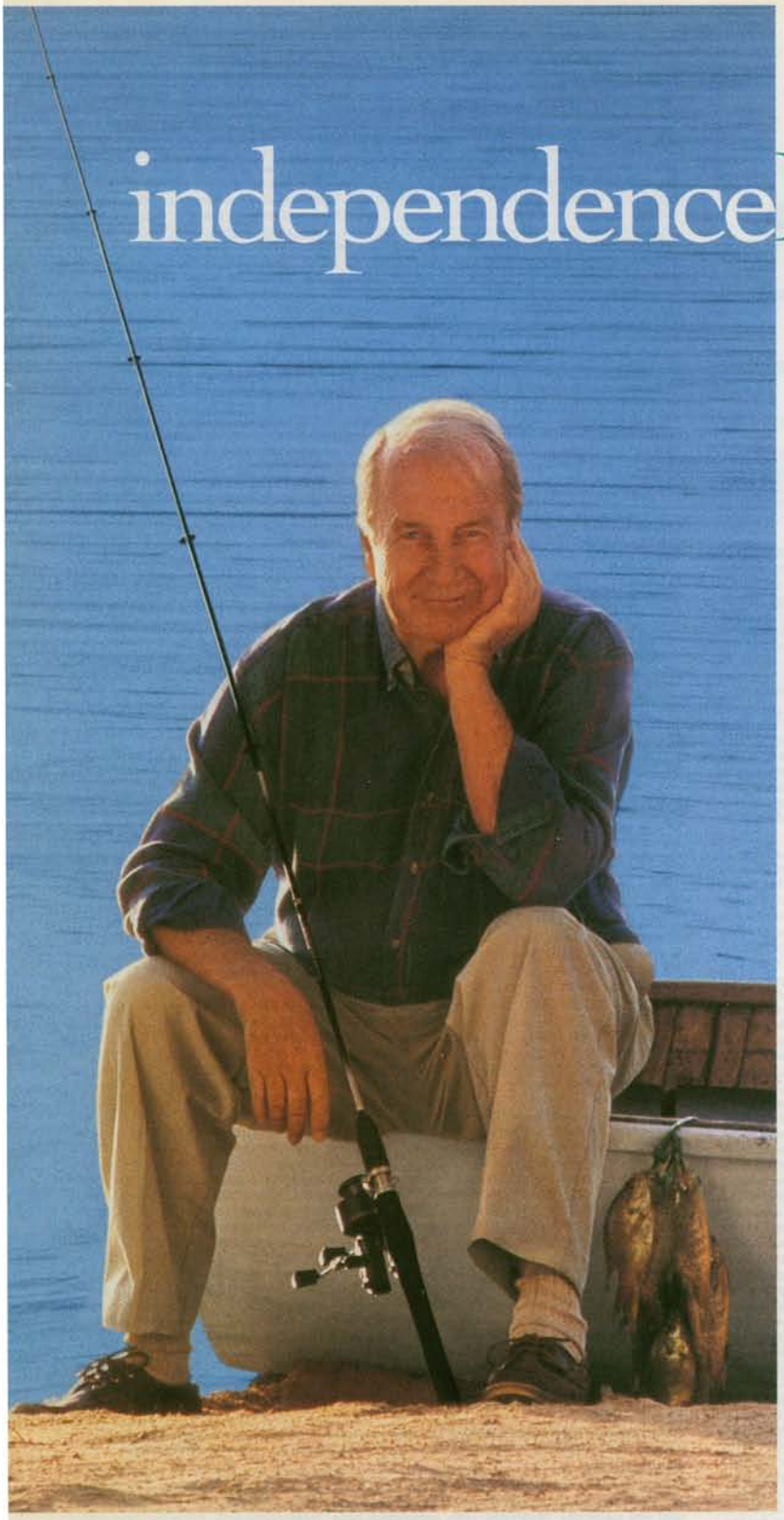

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DAYPRO is indicated for the treatment of the signs and symptoms of OA and RA.

*Usual adult dosage is 1200 mg (two 600-mg caplets) once a day. For osteoarthritis patients of low body weight or with milder disease, an initial dosage of one 600-mg caplet once a day, or an optional one-time loading dose of 1200 mg, may be appropriate. Dosage should be individualized to the lowest effective dose; the maximum recommended total daily dosage is 1800 mg or 26 mg/kg, whichever is *lower,* in divided doses.

Contraindicated in patients with hypersensitivity to DAYPRO or in individuals with nasal polyps, angioedema, or bronchospastic reactivity to aspirin or other NSAIDs. Severe and occasionally fatal asthmatic and anaphylactic reactions to NSAIDs have been reported; there have been rare reports of anaphylaxis with DAYPRO. As with other NSAIDs, the most frequently reported adverse reactions were related to the GI tract. In patients treated chronically with NSAID therapy, serious GI toxicity, such as bleeding, ulceration, and perforation, can occur. Severe renal and hepatic reactions have been reported. There may be a risk of fatal hepatitis with oxaprozin, such as has been seen with other NSAIDs.

Please see brief summary of prescribing information on adjacent page.

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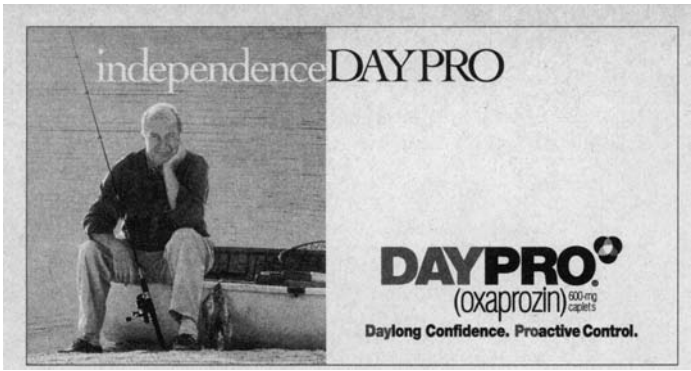

BRIEF SUMMARY— DAYPRO® (oxaprozin) 600-mg caplets

Before prescribing please see full prescribing information.

INDICATIONS AND USAGE: Daypro is indicated for the treatment of the signs and symptoms of OA and RA.

CONTRAINDICATIONS: Hypersensitivity to oxaprozin or any of its components or in individuals with the complete or partial syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). Severe and occasionally fatal asthmatic and anaphylactic reactions have been reported in patients receiving NSAIDs, and there have been rare reports of anaphylaxis in patients taking oxaprozin.

WARNINGS: RISK OF GASTROINTESTINAL (GI) ULCERATION, BLEEDING, AND PERFORATION WITH NONSTEROIDAL ANTI-INFLAMMATORY DRUG THERAPY: Serious gastrointestinal toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Although minor upper gastrointestinal problems, such as dyspepsia, are common, and usually develop early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs, even in the absence of previous GI tract symptoms. In patients observed in clinical trials for several months to 2 years, symptomatic upper GI ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3 to 6 months, and in about 2% to 4% of patients treated for 1 year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur. Patients at risk for developing peptic ulceration and bleeding are those with a prior history of serious GI events, alcoholism, smoking, or other factors known to be associated with peptic ulcer disease. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals, and most spontaneous reports of fatal GI events are in these populations. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, and substantial benefit should be anticipated to patients prior to prescribing maximal doses of Daypro.

PRECAUTIONS: General: ***Hepatic effects:*** As with other NSAIDs, borderline elevations of one or more liver tests may occur in up to 15% of patients. These abnormalities may progress, remain essentially unchanged, or resolve with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of SGOT (AST) occurred in controlled clinical trials of Daypro in just under 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction or in whom an abnormal liver test has occurred should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with this drug. Severe hepatic reactions including jaundice have been reported with Daypro, and there may be a risk of fatal hepatitis with oxaprozin, such as has been seen with other NSAIDs. Although such reactions are rare, if abnormal liver tests persist or worsen, clinical signs and symptoms consistent with liver disease develop, or systemic manifestations occur (eosinophilia, rash, fever), Daypro should be discontinued. Well-compensated hepatic cirrhosis does not appear to alter the disposition of unbound oxaprozin, so dosage adjustment is not necessary. However, the primary route of elimination of oxaprozin is hepatic metabolism, so caution should be observed in patients with severe hepatic dysfunction. ***Renal effects:*** Acute interstitial nephritis, hematuria, and proteinuria have been reported with Daypro as with other NSAIDs. Long-term administration of some NSAIDs to animals has resulted in renal papillary necrosis and other abnormal renal pathology. This was not observed with oxaprozin, but the clinical significance of this difference is unknown. A second form of renal toxicity has been seen in patients with preexisting conditions leading to a reduction in renal blood flow, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with previously impaired renal function, heart failure, or liver dysfunction, those taking diuretics, and the elderly. Discontinuation of NSAID therapy is often followed by recovery to the pretreatment state. Those patients at high risk who chronically take oxaprozin should have renal function monitored if they have signs or symptoms that may be consistent with mild azotemia, such as malaise, fatigue, or loss of appetite. As with all NSAID therapy, patients may occasionally develop some elevation of serum creatinine and BUN levels without any signs or symptoms. The pharmacokinetics of oxaprozin may be significantly altered in patients with renal insufficiency or in patients who are undergoing hemodialysis. Such patients should be started on doses of 600 mg/day, with cautious dosage increases if the desired effect is not obtained. Oxaprozin is not dialyzed because of its high degree of protein binding. Like other NSAIDs, Daypro may worsen fluid retention by the kidneys in patients with uncompensated cardiac failure due to its effect on prostaglandins. It should be used with caution in patients with a history of hypertension, cardiac decompensation, in patients on chronic diuretic therapy, or in those with other conditions predisposing to fluid retention. ***Photosensitivity:*** Oxaprozin has been associated with rash and/or mild photosensitivity in dermatologic testing. An increased incidence of rash on sun-exposed skin was seen in some patients in the clinical trials. ***Recommended laboratory testing:*** Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up (see *Warnings*). Anemia may occur in patients receiving oxaprozin or other NSAIDs. This may be due to fluid retention, gastrointestinal blood loss, or an incompletely described effect upon erythrogenesis. Patients on long-term treatment with Daypro should have their hemoglobin or hematocrit values determined at appropriate intervals as determined by the clinical situation. Oxaprozin, like other NSAIDs, can affect platelet aggregation and prolong bleeding time. Daypro should be used with caution in patients with underlying hemostatic defects or in those who are undergoing surgical procedures where a high degree of hemostasis is needed. **Information for patients:** Daypro, like other drugs of its class, nonsteroidal anti-inflammatory drugs (NSAIDs), is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. NSAIDs are often essential agents in the management of arthritis, but they may also be commonly employed for conditions that are less serious. Physicians may wish to discuss with their patients the potential risks (see *Warnings, Precautions,* and *Adverse Reactions*) and likely benefits of Daypro treatment, particularly in less-serious conditions where treatment without Daypro may represent an acceptable alternative to both the patient and the physician. Patients receiving Daypro may benefit from physician instruction in the symptoms of the more common or serious gastrointestinal, renal, hepatic, hematologic, and dermatologic adverse effects. **Laboratory test interactions:** False-positive urine immunoassay screening tests for benzodiazepines have been reported in patients taking Daypro. This is due to lack of specificity of the screening tests. False-positive test results may be expected for several days following discontinuation of Daypro therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish Daypro from benzodiazepines. **Drug interactions:** *Aspirin:* Concomitant administration of Daypro and aspirin is not recommended because oxaprozin displaces salicylates from plasma protein binding sites. Coadministration would be expected to increase the risk of salicylate toxicity. *Oral anticoagulants:* The anticoagulant effects of warfarin were not affected by the coadministration of 1200 mg/day of Daypro. Nevertheless, caution should be exercised when adding any drug that affects platelet function to the regimen of patients receiving oral anticoagulants. *H_2-receptor antagonists:* The total body clearance of oxaprozin was reduced by 20% in subjects who concurrently received therapeutic doses of cimetidine or ranitidine; no other pharmacokinetic parameter was affected. A change of clearance of this magnitude lies within the range of normal variation and is unlikely to produce a clinically detectable difference in the outcome of therapy. *Beta-blockers:* Subjects receiving 1200 mg Daypro qd with 100 mg metoprolol bid exhibited statistically significant but transient increases in sitting and standing blood pressures after 14 days. Therefore, as with all NSAIDs, routine blood pressure monitoring should be considered in these patients when starting Daypro therapy. *Other drugs:* The coadministration of oxaprozin and antacids, acetaminophen, or conjugated estrogens resulted in no statistically significant changes in pharmacokinetic parameters in single- and/or multiple-dose studies. The interaction of oxaprozin with lithium and cardiac glycosides has not been studied. **Carcinogenesis, mutagenesis, impairment of fertility:** In oncogenicity studies, oxaprozin administration for 2 years was associated with the exacerbation of liver neoplasms (hepatic adenomas and carcinomas) in male CD mice, but not in female CD mice or rats. The significance of this species-specific finding to man is unknown. Oxaprozin did not display mutagenic potential. Results from the Ames test, forward mutation in yeast and Chinese hamster ovary (CHO) cells, DNA repair testing in CHO cells, micronucleus testing in mouse bone marrow, chromosomal aberration testing in human lymphocytes, and cell transformation testing in mouse fibroblast all showed no evidence of genetic toxicity or cell-transforming ability. Oxaprozin administration was not associated with impairment of fertility in male and female rats at oral doses up to 200 mg/kg/day (1180 mg/m^2); the usual human dose is 17 mg/kg/day (629 mg/m^2). However, testicular degeneration was observed in beagle dogs treated with 37.5 to 150 mg/kg/day (750 to 3000 mg/m^2) of oxaprozin for 6 months, or 37.5 mg/kg/day for 42 days, a finding not confirmed in other species. The clinical relevance of this finding is not known. **Pregnancy:** Teratogenic Effects—Pregnancy Category C. There are no adequate or well-controlled studies in pregnant women. Teratology studies with oxaprozin were performed in mice, rats, and rabbits. In mice and rats, no drug-related developmental abnormalities were observed at 50 to 200 mg/kg/day of oxaprozin (225 to 900 mg/m^2). However, in rabbits, infrequent malformed fetuses were observed in dams treated with 7.5 to 30 mg/kg/day of oxaprozin (the usual human dosage range). Oxaprozin should be used during pregnancy only if the potential benefits justify the potential risks to the fetus. **Labor and delivery:** The effect of oxaprozin in pregnant women is unknown. NSAIDs are known to delay parturition, to accelerate closure of the fetal ductus arteriosus, and to be associated with dystocia. Oxaprozin is known to have caused decreases in pup survival in rat studies. Accordingly, the use of oxaprozin during late pregnancy should be avoided. **Nursing mothers:** Studies of oxaprozin excretion in human milk have not been conducted; however, oxaprozin was found in the milk of lactating rats. Since the effects of oxaprozin on infants are not known, caution should be exercised if oxaprozin is administered to nursing women. **Pediatric use:** Safety and effectiveness of Daypro in children have not been established. **Geriatric use:** No adjustment of the dose of Daypro is necessary in the elderly for *pharmacokinetic* reasons, although many elderly may need to receive a reduced dose because of low body weight or disorders associated with aging. No significant differences in the pharmacokinetic profile for oxaprozin were seen in studies in the healthy elderly. Although selected elderly patients in controlled clinical trials tolerated Daypro as well as younger patients, caution should be exercised in treating the elderly, and extra care should be taken when choosing a dose. As with any NSAID, the elderly are likely to tolerate adverse reactions less well than younger patients.

ADVERSE REACTIONS: The most frequently reported adverse reactions were related to the gastrointestinal tract. They were nausea (8%) and dyspepsia (8%). **INCIDENCE GREATER THAN 1%:** In clinical trials the following adverse reactions occurred at an incidence greater than 1% and are probably related to treatment. Reactions occurring in 3% to 9% of patients treated with Daypro are indicated by an asterisk(*); those reactions occurring in less than 3% of patients are unmarked. Abdominal pain/distress, anorexia, constipation*, diarrhea*, dyspepsia*, flatulence, nausea*, vomiting, CNS inhibition (depression, sedation, somnolence, or confusion), disturbance of sleep, *rash**, tinnitus, dysuria or frequency. **INCIDENCE LESS THAN 1%: Probable causal relationship:** The following adverse reactions were reported in clinical trials or from worldwide marketing experience at an incidence of less than 1%. Those reactions reported only from worldwide marketing experience are in *italics.* The probability of a causal relationship exists between the drug and these adverse reactions: Drug hypersensitivity reactions including anaphylaxis *and serum sickness,* edema, blood pressure changes, peptic ulceration and/or GI bleeding (see *Warnings*), liver function abnormalities including *hepatitis* (see *Precautions*), stomatitis, hemorrhoidal or rectal bleeding, *pancreatitis,* anemia, thrombocytopenia, leukopenia, ecchymoses, *agranulocytosis, pancytopenia,* weight gain, weight loss, weakness, malaise, symptoms of upper respiratory tract infection, pruritus, urticaria, photosensitivity, *pseudoporphyria, exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome),* blurred vision, conjunctivitis, *acute interstitial nephritis,* hematuria, renal insufficiency, *acute renal failure,* decreased menstrual flow. ***Causal relationship unknown:*** The following adverse reactions occurred at an incidence of less than 1% in clinical trials, or were suggested from marketing experience, under circumstances where a causal relationship could not be definitely established. They are listed as alerting information for the physician: Palpitations, alteration in taste, sinusitis, pulmonary infections, alopecia, hearing decrease, increase in menstrual flow.

DRUG ABUSE AND DEPENDENCE: Daypro is a non-narcotic drug. Usually reliable animal studies have indicated that Daypro has no known addiction potential in humans.

OVERDOSAGE: No patient experienced either an accidental or intentional overdosage of Daypro in the clinical trials of the drug. Symptoms following acute overdose with other NSAIDs are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain and are generally reversible with supportive care. Gastrointestinal bleeding and coma have occurred following NSAID overdose. Hypertension, acute renal failure, and respiratory depression are rare. Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Gut decontamination may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose (5 to 10 times the usual dose). This should be accomplished via emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) with an osmotic cathartic. Forced diuresis, alkalization of the urine, or hemoperfusion would probably not be useful due to the high degree of protein binding of oxaprozin.

See package insert for complete prescribing information.

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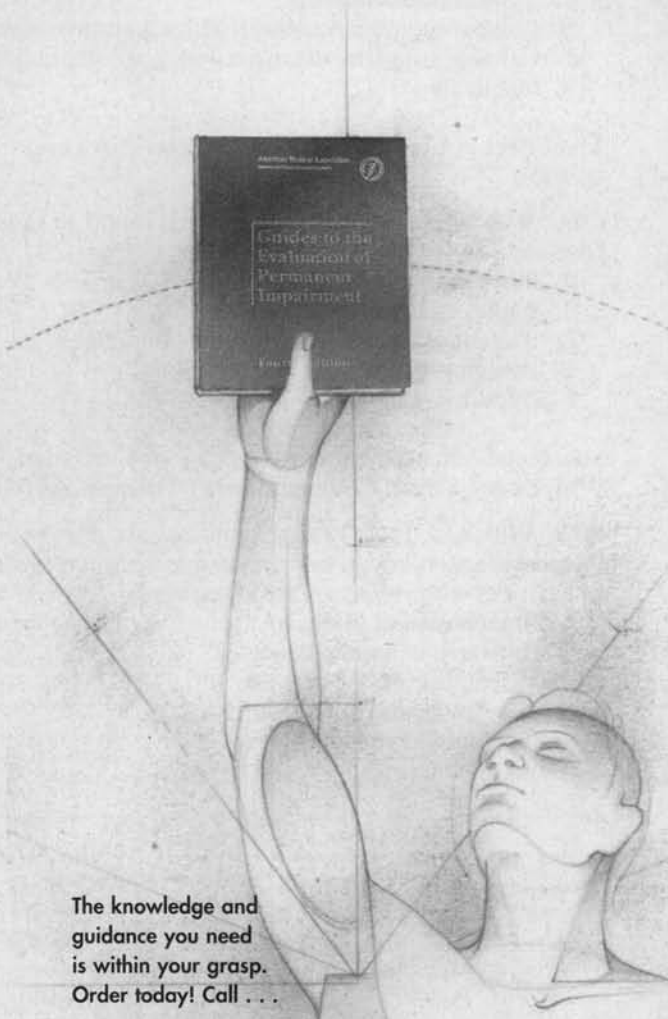

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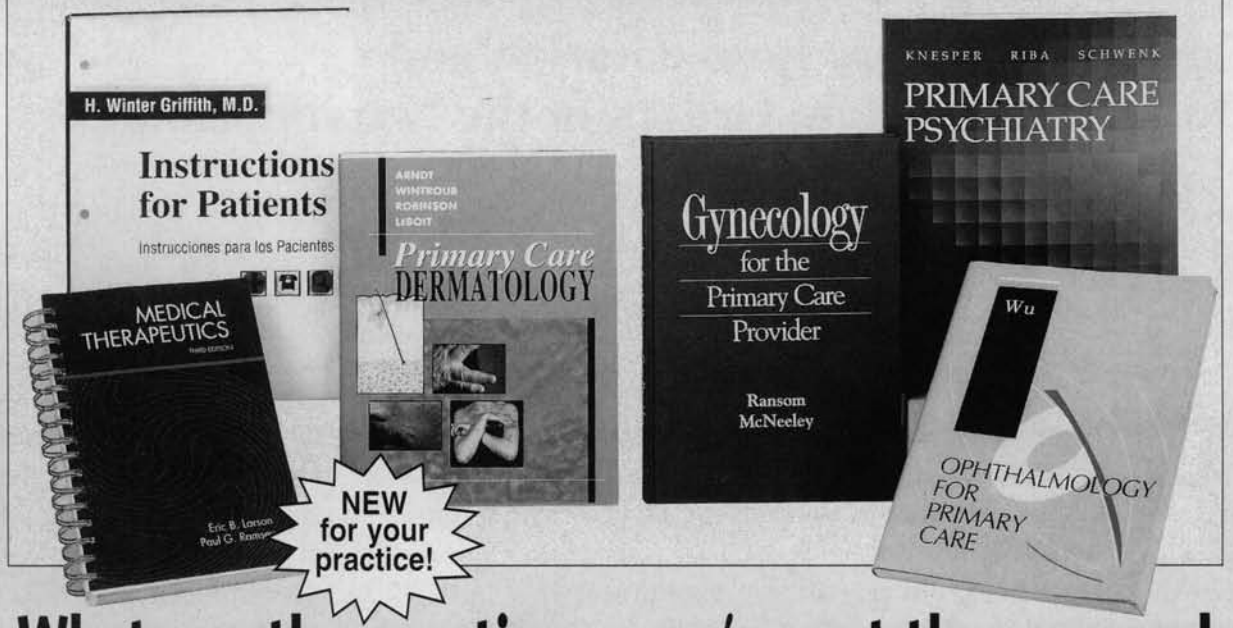

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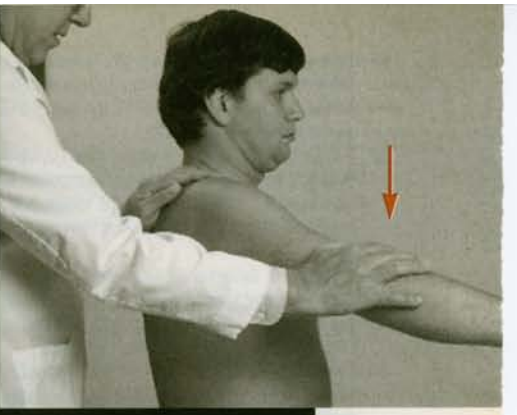
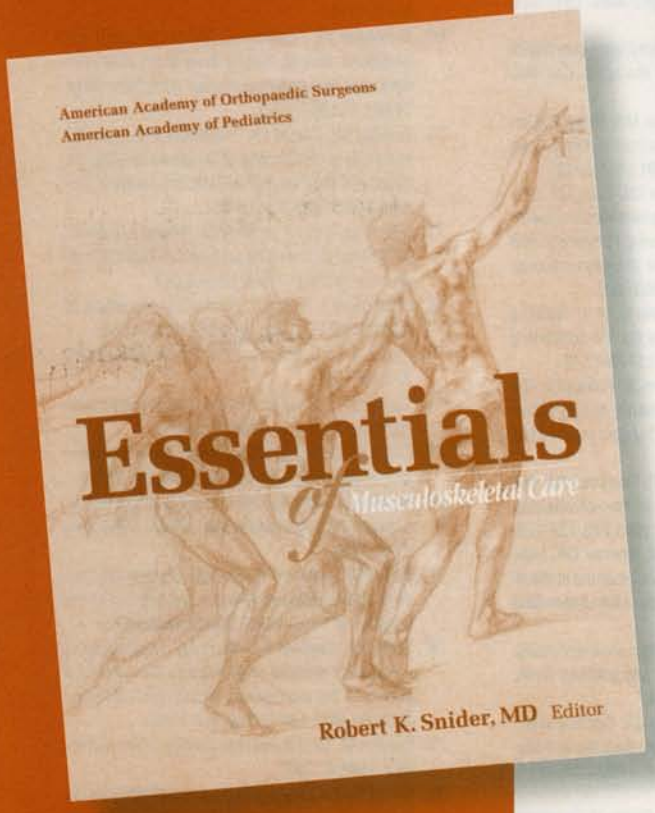


Condition: Impingement Syndrome

INTRODUCING!



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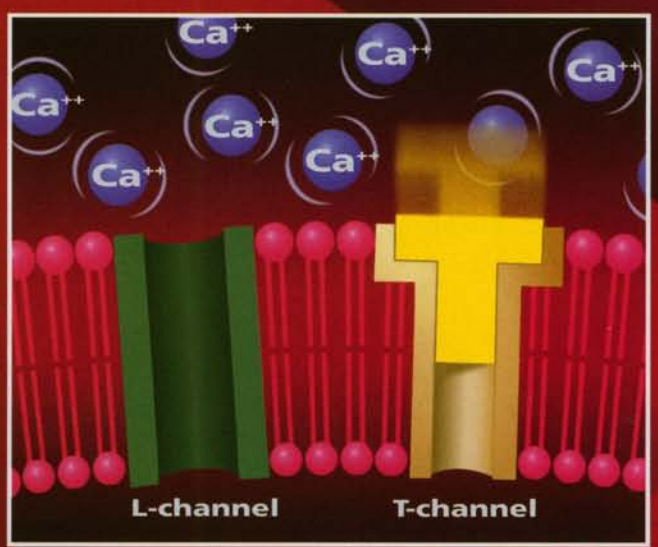
Roche Pharmaceuticals

selectivi-T

of POSICOR

The first and only agent to selectively block T-type calcium channels*[1]

- Current calcium antagonists act primarily on L-type calcium channels[2]
- T-type calcium channels are found in vascular smooth muscle cells, the sinoatrial node, Purkinje cells[2], and neurohormonal secretory cells[3]
- The first of a new class of calcium antagonist in 15 years,[4] a tetralol derivative



Artist's rendition of T-channel blockade at smooth muscle cell membrane.

*Based on animal and in vitro data, POSICOR has been shown to be a T-type calcium channel blocker; however, the clinical significance of this characteristic has not been established at this time.

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References: 1. Mishra SK, Hermsmeyer K. Selective inhibition of T-type Ca2+ channels by RO 40-5967. *Circ Res.* 1994;75: 144-148. **2.** Bean B. Pharmacology of calcium channels in cardiac muscle, vascular muscle, and neurons. *Am J Hypertens.* 1991;4:406S-411S. **3.** Bean B. Classes of calcium channels in vertebrate cells. *Ann Rev Physiol.* 1989; 51:367-384. **4.** IMS America.

safety

of POSICOR

Well-tolerated safety profile

- The only calcium antagonist to induce a slight reduction in heart rate without a negative inotropic effect[5] at therapeutic concentrations[6]
- Provides vasodilation without reflex tachycardia
- Safety regardless of age[7], race, gender, and in patients with renal failure or diabetes, established in studies involving over 3400 patients

Coadministration of POSICOR with terfenadine, astemizole, or cisapride, and in patients with sick sinus syndrome or 2nd or 3rd degree AV block, without a pacemaker, is contraindicated.

Patients with a pretreatment heart rate below 50 bpm should be followed closely. As with all calcium channel blockers, caution should be exercised when treating patients with heart failure or compromised ventricular function. When POSICOR is coadministered with some drugs (e.g., quinidine, sotalol) it may be difficult to use serial ECGs for monitoring the effects of these other drugs.

References: 5. Frishman W. Calcium channel blockers. In: *Cardiovascular Pharmacotherapeutics*. New York, NY:McGraw-Hill Companies, Inc;1997:chap 8. **6.** Rousseau M, Hayashida W, van Eyll C, et al. Hemodynamic and cardiac effects of the selective T-type and L-type calcium channel blocking agent mibefradil in patients with varying degrees of left ventricular systolic dysfunction. *J Am Coll Cardiol*. 1996;28:972-979. **7.** Bursztyn M, Kadr H, Tilvis R, et al. Mibefradil, a novel calcium antagonist, in elderly hypertensives: favorable hemodynamics and pharmacokinetics. Accepted for publication in *Am Heart J*.

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ability

effective management of hypertension

Unsurpassed antihypertensive efficacy

- Effective control of both systolic[8] and diastolic[9] blood pressure
- Consistent, smooth 24-hour control, including early morning hours[9,10]

POSICOR vs Norvasc*

- Unsurpassed antihypertensive efficacy[11,12] with significantly less leg edema (6.8% vs 16.7%, P=0.011)[12]

POSICOR vs Procardia XL†

- Unsurpassed antihypertensive efficacy[13,14] with significantly less leg edema (3.2% vs 10.3%, P=0.027) and headache (0.8% vs 8.7%, P=0.002)[13]

POSICOR vs Cardizem CD‡

- Superior antihypertensive efficacy (P<0.001) with an unsurpassed side effect profile[15,16]

* Norvasc (amlodipine besylate) is a registered trademark of Pfizer.
† Procardia XL (nifedipine GITS) is a registered trademark of Pfizer.
‡ Cardizem CD (diltiazem HCl) is a registered trademark of Hoechst Marion Roussel.

References: 8. Data on file (Ref. 074-007), Hoffmann-La Roche Inc., Nutley, New Jersey 07110. **9.** Oparil S, Kobrin I, Abernethy D, et al. Dose-response characteristics of mibefradil, a novel calcium antagonist, in the treatment of essential hypertension. Accepted for publication in *Am J. Hypertens*. **10.** Schmitt R, Kleinbloesem C, Belz G, et al. Hemodynamic and humoral effects of the novel calcium antagonist RO 40-5967 in patients with hypertension. *Clin Pharmacol Ther.* 1992;52: 314-323. **11.** Viskoper R, Bernink P, Ziekenhuis M, et al. A randomized, double-blind trial comparing mibefradil and amlodipine: two long-acting calcium antagonists with similar efficacy but different tolerability profiles. Accepted for publication in *J Human Hypertens*. **12.** Data on file (Ref. 074-008), Hoffmann-La Roche Inc., Nutley, New Jersey 07110. **13.** Data on file (Ref. 074-009), Hoffmann-La Roche Inc., Nutley, New Jersey 07110. **14.** Data on file (Ref. 074-010), Hoffmann-La Roche Inc., Nutley, New Jersey 07110. **15.** Massie B, Chrysant S, Jain A, Weir M, Weiss R, Kobrin I. Antihypertensive effects of mibefradil: a double-blind comparison with diltiazem CD. *Clin Cardiol*. 1997;20:562-568. **16.** Data on file (Ref. 074-015), Hoffmann-La Roche Inc., Nutley, New Jersey 07110.

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tolerability

comparable to placebo

Excellent tolerability profile at both doses

- Does not cause constipation[17]

Compare the tolerability of POSICOR to placebo			
Adverse Event	Placebo (n=283)	POSICOR 50 mg (n=279)	POSICOR 100 mg (n=285)
Headache	6%	3%	8%
Leg Edema	3%	1%	4%
Rhinitis	0%	3%	3%
Abdominal Pain	1%	1%	2%
Light-headed Feeling	0%	1%	3%
Dyspepsia	1%	1%	2%

Coadministration of POSICOR with terfenadine, astemizole, or cisapride, and in patients with sick sinus syndrome or 2nd or 3rd degree AV block, without a pacemaker, is contraindicated. Patients with a pretreatment heart rate below 50 bpm should be followed closely. As with all calcium channel blockers, caution should be exercised when treating patients with heart failure or compromised ventricular function.
When POSICOR is coadministered with some drugs (e.g., quinidine, sotalol) it may be difficult to use serial ECGs for monitoring the effects of these other drugs.

Reference: 17. Data on file (Ref. 074-013), Hoffmann-La Roche Inc., Nutley, New Jersey 07110.

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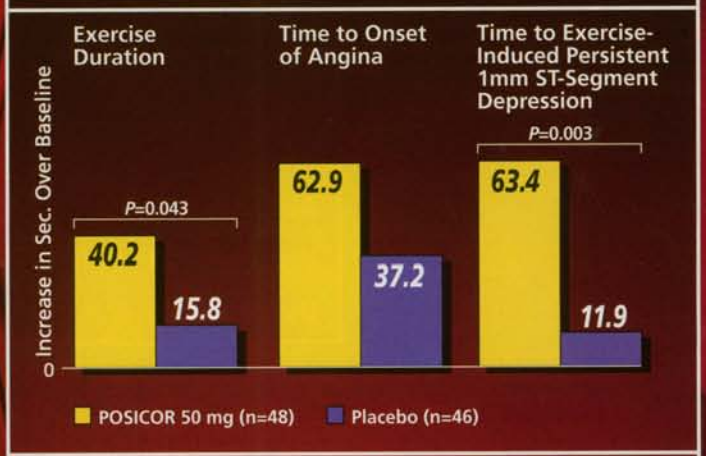
activity

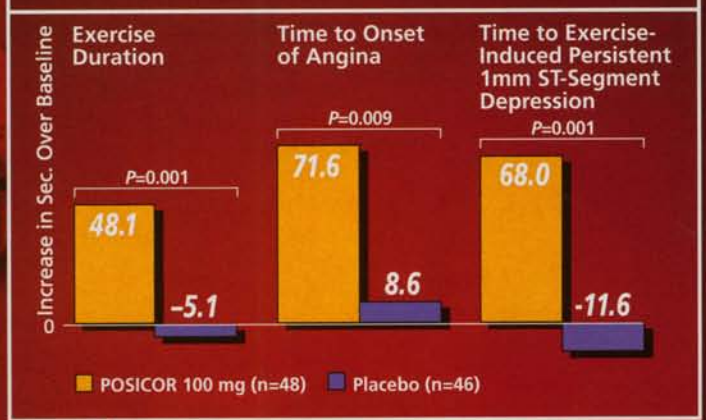
improves ETT parameters

Consistent control of angina

Used alone[18] or in combination with beta-blockers[19,20] or nitrates[21]

POSICOR vs Placebo with existing beta-blocker therapy in Exercise Tolerance Test (ETT) parameters*[20]





*Study Design: 4-week, randomized, double-blind, placebo-controlled
Exercise Duration Baseline:
POSICOR (343.1 sec) Placebo (350.7 sec)
Time to Onset of Angina Baseline:
POSICOR (262.1 sec) Placebo (272.6 sec)
Time to Exercise-Induced Persistent 1mm ST-Segment Depression Baseline: POSICOR (281.5 sec) Placebo (287.5 sec)

References: 18. Bakx A, van der Wall E, Braun S, Emanuelsson H, Bruschke A, Kobrin I. Effects of the new calcium antagonist mibefradil (RO 40-5967) on exercise duration in patients with chronic stable angina pectoris: a multicenter, placebo-controlled study. *Am Heart J.* 1995; 130:748-757. **19.** Alpert J, Kobrin I, DeQuattro V, et al. Additional antianginal and anti-ischemic efficacy of mibefradil in patients pretreated with a beta blocker for chronic stable angina pectoris. *Am J Cardiol.* 1997;79:1025-1030. **20.** Schneeweiss A, Kobrin I, Caspi A, et al. Adding the new calcium antagonist mibefradil to patients on chronic ß-blocker therapy results in improved anti-anginal and anti-ischemic efficacy. Submitted for publication in *Am Heart J.* **21.** Data on file (Ref. 074-011), Hoffmann-La Roche Inc., Nutley, New Jersey 07110.

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Selectivity

- The first and only agent to selectively block T-type calcium channels[1]

Safety

- The only calcium antagonist to induce a slight reduction in heart rate without a negative inotropic effect[5] at therapeutic concentrations[6]
- Provides vasodilation without reflex tachycardia

Ability

- Effective control of hypertension
- Unsurpassed antihypertensive efficacy vs Norvasc[11,12] and Procardia XL[13,14]
- Superior antihypertensive efficacy vs Cardizem CD[15,16]

Tolerability

- Comparable to placebo

Activity

- Consistent control of angina; improves ETT parameters[22]

Coadministration of POSICOR with terfenadine, astemizole, or cisapride, and in patients with sick sinus syndrome or 2nd or 3rd degree AV block, without a pacemaker, is contraindicated. Patients with a pretreatment heart rate below 50 bpm should be followed closely. As with all calcium channel blockers, caution should be exercised when treating patients with heart failure or compromised ventricular function.

When POSICOR is coadministered with some drugs (e.g., quinidine, sotalol) it may be difficult to use serial ECGs for monitoring the effects of these other drugs.

It may be necessary to adjust the dose of other drugs metabolized by Cytochrome P450 3A4 or 2D6 when given concomitantly with POSICOR. It is recommended to adjust the dose of tricyclic antidepressants and to monitor the levels of cyclosporine A when given concomitantly with POSICOR.

References: 1. Mishra SK, Hermsmeyer K. Selective inhibition of T-type Ca2+ channels by RO 40-5967. *Circ Res.* 1994;75: 144-148. **5.** Frishman W. Calcium channel blockers. In: *Cardiovascular Pharmacotherapeutics*. New York, NY:McGraw-Hill Companies, Inc;1997:chap 8. **6.** Rousseau M, Hayashida W, van Eyll C, et al. Hemodynamic and cardiac effects of the selective T-type and L-type calcium channel blocking agent mibefradil in patients with varying degrees of left ventricular systolic dysfunction. *J Am Coll Cardiol.* 1996:28:972-979. **11.** Viskoper R, Bernink P, Ziekenhuis M, et al. A randomized, double-blind trial comparing mibefradil and amlodipine: two long-acting calcium antagonists with similar efficacy but different tolerability profiles. Accepted for publication in *J Human Hypertens*. **12.** Data on file (Ref. 074-008), Hoffmann-La Roche Inc., Nutley, New Jersey 07110. **13.** Data on file (Ref. 074-009), Hoffmann-La Roche Inc., Nutley, New Jersey 07110. **14.** Data on file (Ref. 074-010), Hoffmann-La Roche Inc., Nutley, New Jersey 07110. **15.** Massie B, Chrysant S, Jain A, Weir M, Weiss R, Kobrin I. Antihypertensive effects of mibefradil: a double-blind comparison with diltiazem CD. *Clin Cardiol.* 1997;20:562-568. **16.** Data on file (Ref. 074-015), Hoffmann-La Roche Inc., Nutley, New Jersey 07110. **22.** Tzivoni D, Kadr H, Braat S, et al. Efficacy of mibefradil in comparison to amlodipine in suppressing exercise-induced and daily silent ischemia: results of a multicenter, placebo-controlled trial. Accepted for publication in *Circulation*.

17-090-074-004-077

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Before prescribing, please see complete product information, a summary of which follows.

DESCRIPTION: POSICOR® (mibefradil dihydrochloride) is a selective T-type calcium channel ion influx inhibitor.

INDICATIONS AND USAGE: POSICOR is indicated for the treatment of hypertension or chronic stable angina pectoris. POSICOR can be used alone or in combination with other antihypertensive agents or antianginal agents.

OVERDOSAGE: At present there has been no experience with single doses >350 mg or multiple doses >250 mg. Doses higher than these might cause excessive peripheral vasodilation with marked hypotension, bradycardia and/or high-degree AV block. If a patient is suspected of having taken an overdose, continuous ECG monitoring and repeated blood pressure measurements should be instituted. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium antagonists. As mibefradil is highly bound to plasma proteins, it cannot be removed by dialysis.

Bradycardia and high-degree AV block may be treated with atropine, isoproterenol and cardiac pacing.

DOSAGE AND ADMINISTRATION: The recommended doses of POSICOR are 50 mg and 100 mg once daily. The larger dose is, on average, more effective. Doses above 100 mg offer little or no additional benefit and induce a greater rate of adverse reactions. POSICOR can be taken with or without food. Tablets should be swallowed and not chewed or crushed.

Coadministration with Other Antihypertensive and/or Antianginal Drugs: POSICOR has been safely administered with diuretics, ACE inhibitors, beta-blockers, long-acting nitrates and sublingual nitroglycerin.

Administration in Subpopulations: POSICOR has been used safely in patients regardless of age, race, gender, and body weight and in those with common concomitant diseases, such as chronic renal failure, chronic obstructive pulmonary disease and diabetes mellitus. However, caution should be exercised in patients with severe hepatic impairment.

CONTRAINDICATIONS: POSICOR is contraindicated in patients with:

1. Sick sinus syndrome or second- or third-degree AV block, without a pacemaker;
2. A known sensitivity to mibefradil;
3. Coadministration of terfenadine, astemizole and cisapride.

WARNING: Mibefradil may cause dose-related changes in the appearance of the electrocardiographic T and U waves. These changes may interfere with measurement of the QTc interval. Some drugs (eg, quinidine, sotalol) are sometimes monitored by following the QTc interval on serial electrocardiograms, in order to reduce the risk of torsades de pointes and other malignant arrhythmias. When mibefradil is coadministered with these drugs, it may be difficult to utilize serial electrocardiograms for this purpose.

PRECAUTIONS: ***General:*** POSICOR inhibits cytochrome P450 2D6 and 3A4 and can interact with many concomitant drugs, increasing their plasma concentrations (see *Drug Interactions*).

Hypotension: Although hypotension, postural hypotension, and syncope have been only rarely associated with POSICOR, and are not clearly more common than with placebo, caution should be exercised when administering POSICOR, particularly to patients with severe aortic stenosis.

Use in Patients with Congestive Heart Failure: Acute hemodynamic studies in a small number of patients with ischemic heart disease with or without impaired cardiac function treated with POSICOR have not demonstrated negative inotropic effects, nor was POSICOR associated with reflex tachycardia or an increase in neurohormones. Long-term studies in patients with moderate to severe (NYHA III, IV) heart failure have not been carried out. As with all calcium antagonists, caution should be exercised when treating patients with heart failure or compromised ventricular function.

Patients with Hepatic Failure: Since mibefradil is extensively metabolized by the liver, caution should be exercised when administering POSICOR to patients with severe hepatic impairment.

Cardiac Conduction: As described under CLINICAL PHARMACOLOGY, POSICOR slows sinus and AV node conduction, sometimes resulting in abnormally low heart rates; 0.7% and 1.4% of patients had heart rates below 45 bpm on 50 mg and 100 mg, respectively. Therefore, patients with a pretreatment heart rate below 50 bpm should be followed closely. Treatment with POSICOR has rarely been associated with second-degree AV block, 0.2% of patients on doses of 50 mg to 100 mg. No cases of third-degree AV block have been reported at 50 mg to 100 mg, but at higher doses third-degree AV block can rarely occur.

Drug Interactions: *Effects of Other Drugs on Mibefradil Pharmacokinetics:* No clinically relevant changes in pharmacokinetics of mibefradil have been seen in specific studies when mibefradil was coadministered with enalapril, atenolol, metoprolol, theophylline and cimetidine.

Effects of Mibefradil on the Pharmacokinetics of Other Drugs: **Interactions with Drugs Metabolized by Cytochrome P450 Enzymes:** In vitro results indicate that some isozymes of the cytochrome P450 enzyme system, including 2D6, 1A2, and 3A4, are inhibited in the presence of mibefradil or its metabolites. Coadministration of POSICOR with drugs metabolized by these isozymes may result in increased plasma concentrations of these drugs.

Drugs Metabolized by Cytochrome P450 2D6: A subset (about 7%) of the white population and 1% and 2% of Orientals and blacks, respectively, have reduced activity of the drug-metabolizing isozyme cytochrome P450 2D6 (debrisoquine hydroxylase). Such individuals are referred to as "poor metabolizers" of such drugs as dextromethorphan, the type 1C antiarrhythmics propafenone, flecainamide and mexiletine, some beta-blockers and tricyclic antidepressants (particularly those with high first-pass effect, ie, desipramine and imipramine). Poor metabolizers have higher than expected plasma concentrations of such drugs when given in usual doses. Depending on the fraction of the drug metabolized by cytochrome P450 2D6, the increase in plasma concentration may be small or quite large. POSICOR, like several other drugs, inhibits the activity of this isozyme and can make previously normal metabolizers resemble poor metabolizers. Concomitant use of POSICOR with drugs metabolized by cytochrome P450 2D6 may require dose adjustment of the other drugs.

Tricyclic Antidepressants: Imipramine and desipramine have been shown to have substantial (seven- to eightfold) increases in AUC when CYP 450 2D6 metabolism is inhibited; concomitant use of tricyclic antidepressants with POSICOR would require substantial dose adjustment of the tricyclic antidepressant.

Drugs Metabolized by Cytochrome P450 3A4: POSICOR and/or its metabolites also inhibit the activity of cytochrome P450 3A4, an enzyme responsible for the metabolism of many drugs, including quinidine, short-acting benzodiazepines, most calcium-channel blockers, terfenadine, astemizole and cisapride. POSICOR may increase plasma concentrations of coadministered drugs that are primarily metabolized by the cytochrome P450 3A4 enzyme system and may consequently increase or prolong their therapeutic and adverse effects. Therefore, unless otherwise specified, dosage adjustment of these drugs may be necessary. For drugs that can cause serious adverse effects if concentration is increased, concomitant use with POSICOR should be avoided (see CONTRAINDICATIONS).

The following drug interactions have been identified involving mibefradil and other drugs metabolized by the cytochrome P450 system:

Terfenadine: Coadministration of terfenadine (metabolized by CYP 450 3A4) with POSICOR in healthy subjects led to elevated plasma concentrations of terfenadine up to 40 ng/mL with twice-daily dosing of 60 mg terfenadine, resulting in a 12% increase in mean QTc interval. Since QTc prolongation due to elevated plasma concentrations of terfenadine can be associated with life-threatening cardiac dysrhythmias and death, coadministration of POSICOR with terfenadine is contraindicated (see CONTRAINDICATIONS).

Astemizole and Cisapride: Although there are no specific studies of interaction of mibefradil with these drugs, substantial inhibition of their metabolism would be expected. Since elevated plasma concentrations of astemizole and cisapride can be associated with life-threatening cardiac dysrhythmias, their use with mibefradil is contraindicated. One such case has been observed in a patient receiving cisapride and concomitant mibefradil.

Cyclosporine A: Cyclosporine A (Sandimmune®), a drug metabolized by CYP 450 3A4, levels increased about twofold under concomitant treatment with 50 mg POSICOR for eight days. Therefore, cyclosporine A levels should be monitored and its dose adjusted accordingly.

Quinidine: In healthy volunteers, elevations in peak quinidine plasma concentrations (15% to 19%) and AUC (50%) were found during coadministration of single doses of quinidine with POSICOR 50 mg and 100 mg, but the active metabolite of quinidine was markedly reduced. No clinically relevant pharmacodynamic interactions were observed.

Metoprolol: Coadministration of POSICOR with metoprolol (metabolized by CYP 450 2D6) in healthy subjects resulted in a twofold increase in peak plasma concentrations of total (R- and S-enantiomeric) metoprolol and about four- to fivefold increase in AUC. Elimination half-life increased from three hours to seven to eight hours. The increase in the pharmacologically more active S-isomer, however, is only about 30%, so that little pharmacologic effect or effect on cardioselectivity would be expected with concomitant POSICOR.

Other Information: In clinical studies, POSICOR has been administered without apparent harm with commonly used drugs including diuretics, beta-blockers, ACE inhibitors, nonsteroidal antiinflammatory drugs, long-acting nitrates, sublingual nitroglycerin, oral hypoglycemics, fibrate lipid-lowering agents, conjugated estrogens, antibiotics and antithrombotics. CYP 450 3A4 mediates the metabolism of several HMG CoA reductase inhibitors. Use of these drugs has been associated with rhabdomyolysis, which may be more frequent when they are coadministered with drugs that inhibit CYP 450 3A4. Although no such adverse interaction has been seen with POSICOR, the possibility should be considered.

Specific Interaction Studies: In specific studies, no clinically relevant interactions have been observed between the recommended doses of POSICOR and enalapril, atenolol or cimetidine. Despite in vitro evidence of inhibition of CYP 450 1A2, no pharmacokinetic interaction was observed with theophylline, a CYP 450 1A2 substrate. In healthy volunteers, small elevations in digoxin peak plasma levels (20% to 30%) were found during coadministration with POSICOR 50 mg and 100 mg, but trough plasma levels were unchanged in these volunteers and in patients with congestive heart failure.

Protein Binding: Mibefradil is highly protein bound (99.5%), mainly to alpha$_1$-acid glycoprotein (95%). Therefore, it will not displace drugs which bind to serum albumin, such as warfarin, phenytoin and digoxin.

Information for Patients: Patients should be instructed to take POSICOR whole and not to crush or chew the tablet. Patients should inform their physicians if they are pregnant or plan to become pregnant or are breast-feeding. Patients should be informed that light-headedness or fatigue can occur and that these symptoms should be reported to a physician.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Mibefradil was not mutagenic in the Ames microbial mutagenicity test with or without metabolic activation, in the microbial test with E. coli or in Chinese hamster V79 cells. No genotoxicity was observed in a test of unscheduled DNA synthesis in rat primary hepatocytes, and no chromosomal damage was observed in a test of human peripheral blood lymphocytes treated in vitro or in an in vivo micronucleus test.

A decrease in mating incidence and a prolongation of time to mating was observed when male and female rats were treated with mibefradil dihydrochloride at a daily dose of 39 mg mibefradil/kg (approximately three times the maximum recommended human dose [MRHD] on a mg/m^2 basis) prior to and during the mating period. For those females successfully mated at this dose, there was a decrease in fetuses/dam observed at caesarean section or pups/dam at natural delivery, findings associated with both a decrease in number of corpora lutea per dam (evidence of a decrease in ovulation) and an increase in preimplantation loss (ovulations not resulting in implants).

Oral gavage administration of mibefradil dihydrochloride to male mice for up to 95 weeks and to female mice for up to 104 weeks at doses up to 65 mg mibefradil/kg/day (about three times the MRHD of 100 mg mibefradil/day on a mg/m^2 basis) revealed no evidence of a carcinogenic effect of mibefradil. When administered in the feed of rats at doses of 35 mg mibefradil/kg/day (about three times the MRHD on a mg/m^2 basis) for up to 104 weeks, an increased incidence of squamous cell carcinoma of the oral cavity was observed. A similar association was observed when another rat study was conducted with similar doses of mibefradil administered by gavage. The latter study, which evaluated diet as a risk factor for the oral cavity tumors, demonstrated that the carcinogenic effect of mibefradil was dependent on the aggressiveness (in terms of producing severe periodontitis) of the diet employed combined with class-related gingival overgrowth. No tumors were observed when mibefradil was administered to rats fed a less aggressive diet associated with much lower levels of periodontitis.

Pregnancy: Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. POSICOR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: POSICOR should be avoided during the time of expected labor and during parturition.

Nursing Mothers: Administration of mibefradil should be avoided, if possible, in lactating women who continue to nurse.

Pediatric Use: Safety and effectiveness of POSICOR in pediatric patients have not been established.

ADVERSE REACTIONS: POSICOR has been evaluated for safety in 3430 patients (2194 with hypertension, 1236 with chronic stable angina pectoris). In general, treatment with POSICOR was well tolerated at doses up to 100 mg daily. Most adverse reactions associated with POSICOR were transient and of mild or moderate intensity. In placebo-controlled clinical trials, the rate of discontinuation of POSICOR (50 mg and 100 mg) due to adverse reactions was similar to that of placebo. Discontinuation due to dizziness was the only reason for premature withdrawal that was more common on mibefradil than on placebo. In the pooled placebo-controlled hypertension and chronic stable angina pectoris trials that studied doses of 50 mg/day and 100 mg/day, the incidence of adverse experiences present in at least 1% of patients treated with the 100 mg dose and more common on that dose than on placebo were:

	POSICOR		
	Placebo (N=283)	50 mg (N=279)	100 mg (N=285)
Headache	6%	3%	8%
Leg Edema	3%	1%	4%
Rhinitis	0%	3%	3%
Abdominal Pain	1%	1%	2%
Light-headed Feeling	0%	1%	3%
Dyspepsia	1%	1%	2%

The following adverse experiences were also present in >1% of patients treated with the 100 mg dose but occurred at a frequency equal to or less than placebo: allergic reaction, angina pectoris, dizziness, fatigue, flushing, influenza, palpitations, upper respiratory tract infection and vomiting/nausea.

The following adverse experiences occurred in a dose-related manner in placebo-controlled trials over a dose range of 50 mg to 150 mg: dizziness, dyspepsia, flushing, leg edema, rhinitis and vomiting/nausea.

There were no clinically important differences in the effect of POSICOR on adverse experience rates based on age, gender or race.

In the 2636 patients treated with POSICOR (50 mg or 100 mg) in controlled or uncontrolled trials, the following adverse experiences, whether drug related or not, occurred at a frequency greater than 0.5% or occurred at a lower rate but were potentially important:

Autonomic Nervous System: increased sweating, orthostatic complaints, postural hypotension, syncope; *Body as a Whole:* generalized weakness, trauma; *Cardiovascular:* bradycardia, cardiac failure, chest pain nonspecific, hypotension; *Central and Peripheral Nervous System:* paresthesia; *Gastrointestinal:* constipation, diarrhea, flatulence, gastroenteritis, rectal hemorrhage; *Hearing and Vestibular:* ear buzzing, otitis; *Immunologic:* angioedema; *Musculoskeletal:* arthritis, back pain, chest pain, muscle cramps, pain of extremities, sprains and strains; *Psychiatric:* anxiety, depression, insomnia; *Reproductive, Male:* impotence; *Respiratory:* bronchitis, coughing, dyspnea, nasal congestion, pharyngitis, sinusitis; *Skin and Appendages:* exfoliative dermatitis, rash; *Urinary System:* urinary tract infection; *Vision:* conjunctivitis.

Electrocardiographic Changes: Treatment emergent ECG changes that clearly occurred in a dose-related manner in the placebo-controlled trials were bradycardia (heart rate < 45 bpm): 0.7% (50 mg) and 1.4% (100 mg) and first-degree AV block: 3.6% (50 mg) and 8.4% (100 mg). In the 2636 patients treated with POSICOR (50 mg or 100 mg) in controlled or uncontrolled trials, second-degree AV block was recorded in 0.2% of the patients.

POSICOR therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in hematology parameters, serum potassium, sodium, calcium, glucose, plasma lipids, uric acid, urea nitrogen, creatinine or liver function tests.

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POSICOR® (mibefradil dihydrochloride)

Roche Pharmaceuticals

Roche Laboratories Inc.
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Nutley, New Jersey 07110-1199

POSICOR® (mibefradil dihydrochloride)

ONCE-A-DAY CARDIZEM® CD

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

℞ Cardizem CD Start with one 180-mg capsule daily and titrate as necessary

Brief Summary of
Prescribing Information as of December 1995A

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. (See ADVERSE REACTIONS section.)
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 pediatric patients 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: allergic reactions, alopecia, angioedema (including facial or periorbital edema), asystole, erythema multiforme (including Stevens-Johnson syndrome, toxic epidermal necrolysis), 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, some 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 December 1995A

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References: 1. Massie BM, Der E, Herman TS, Topolski P, Park GD, Stewart WH. *Clin Cardiol.* 1992;15:365-368. **2.** Data on file, Hoechst Marion Roussel. **3.** Procardia XL® prescribing information. **4.** Norvasc® prescribing information. **5.** Sular® prescribing information.

97262201/1917M7

CARDIZEM® CD

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

In Hypertension

- In a randomized, double-blind study of 127 hypertensives, 86% of patients reaching goal of blood pressure on CARDIZEM CD were controlled at 240 mg or less.[1]

In Angina

- CARDIZEM CD is effective as monotherapy and adds efficacy to beta-blocker and/or nitrate therapy .[2]*

Safety

- Unlike many short-acting and long-acting dihydropyridine products (nifedipine, amlodipine, nisoldipine), no warnings for increased incidence (rare) of myocardial infarction.[3-5]
- Most commonly reported side effects are headache (5.4%), bradycardia (3.3%), first-degree AV block (3.3%), dizziness (3.0%), edema (2.6%), asthenia (1.8%), and ECG abnormality (1.6%).

* Experience with use of CARDIZEM in combination with beta-blockers in patients with impaired ventricular function is limited. Available data are not sufficient to predict the effects of concomitant treatment with CARDIZEM CD and beta-blockers in patients with left ventricular dysfunction of cardiac conduction abnormalities. Caution should be exercised when using this combination. (See Warnings and Precautions in prescribing information.)

97262201/1917M7

Please see brief summary of prescribing information on adjacent page.