



Give allergic noses relief for itchy eyes due to seasonal allergic conjunctivitis.

When seasonal allergies strike, it's not just the nose they ambush. The eyes are fair game, too. In fact, 8 out of 10 patients with allergic noses also suffer from itchy eyes¹ due to seasonal allergic conjunctivitis. Stop the itch with ACULAR[®] Solution.

In a recent survey (n=272), the vast majority of responding patients confirmed that ACULAR[®] stopped their ocular itching quickly and effectively.² Plus, ACULAR[®] has a favorable safety profile. There are no steroid-like side effects that can alter intraocular pressure, and no decongestant-like side effects, i.e., no risk to patients with narrow chamber angles.

So help rescue eyes from itching with ACULAR[®], the #1 prescribed ophthalmic preparation³ for the #1 patient complaint of seasonal allergic conjunctivitis — ocular itch. Because annoying antigens prey on more than just the nose.

The most frequently reported adverse events have been transient stinging and burning on instillation (approximately 40%). Not for use while wearing soft contact lenses.

STOPS THE ITCH
ACULAR[®]

(ketorolac tromethamine) 0.5%
Sterile Ophthalmic Solution

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Irvine, CA 92715

FISONS
Pharmaceuticals

Fisons Corporation
Rochester, NY 14623 U.S.A.

Please see adjacent page for prescribing information.

ACULAR® (ketorolac tromethamine) 0.5% Sterile Ophthalmic Solution

INDICATIONS AND USAGE

ACULAR® ophthalmic solution is indicated for the relief of ocular itching due to seasonal allergic conjunctivitis.

CONTRAINDICATIONS

ACULAR® ophthalmic solution is contraindicated in patients while wearing soft contact lenses and in patients with previously demonstrated hypersensitivity to any of the ingredients in the formulation.

WARNINGS

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other nonsteroidal anti-inflammatory agents. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

With some nonsteroidal anti-inflammatory drugs, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

PRECAUTIONS

General: It is recommended that ACULAR® ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: An 18-month study in mice at oral doses of ketorolac tromethamine equal to the parenteral MRHD (Maximum Recommended Human Dose) and a 24-month study in rats at oral doses 2.5 times the parenteral MRHD, showed no evidence of tumorigenicity. Ketorolac tromethamine was not mutagenic in Ames test, unscheduled DNA synthesis and repair, and in forward mutation assays. Ketorolac did not cause chromosome breakage in the *in vivo* mouse micronucleus assay. At 1590 µg/mL (approximately 1000 times the average human plasma levels) and at higher concentrations ketorolac tromethamine increased the incidence of chromosomal aberrations in Chinese hamster ovarian cells. Impairment of fertility did not occur in male or female rats at oral doses of 9 mg/kg (53.1 mg/m²) and 16 mg/kg (94.4 mg/m²) respectively.

Pregnancy: Pregnancy Category C. Reproduction studies have been performed in rabbits, using daily oral doses at 3.6 mg/kg (42.35 mg/m²) and in rats at 10 mg/kg (59 mg/m²) during organogenesis. Results of these studies did not reveal evidence of teratogenicity to the fetus. Oral doses of ketorolac tromethamine at 1.5 mg/kg (8.8 mg/m²), which was half of the human oral exposure, administered after gestation day 17 caused dystocia and higher pup mortality in rats. There are no adequate and well-controlled studies in pregnant women. Ketorolac tromethamine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Caution should be exercised when ACULAR® is administered to a nursing woman.

Pediatric Use: Safety and efficacy in children have not been established.

ADVERSE REACTIONS

In patients with allergic conjunctivitis, the most frequent adverse events reported with the use of ACULAR® ophthalmic solution have been transient stinging and burning on instillation. These events were reported by approximately 40% of patients treated with ACULAR® ophthalmic solution. In all development studies conducted, other adverse events reported during treatment with ACULAR® include ocular irritation (3%), allergic reactions (3%), superficial ocular infections (0.5%) and superficial keratitis (1%).

ACULAR®, a registered trademark of Syntex (U.S.A.) Inc, is manufactured and distributed by Allergan, Inc. under license from its developer, Syntex (U.S.A.) Inc., Palo Alto, California, U.S.A.

REFERENCES: 1. Data on file, Fisons Corporation, 1985. 2. Data on file, Allergan, Inc., 1994. 3. IMS Data, December, 1994.

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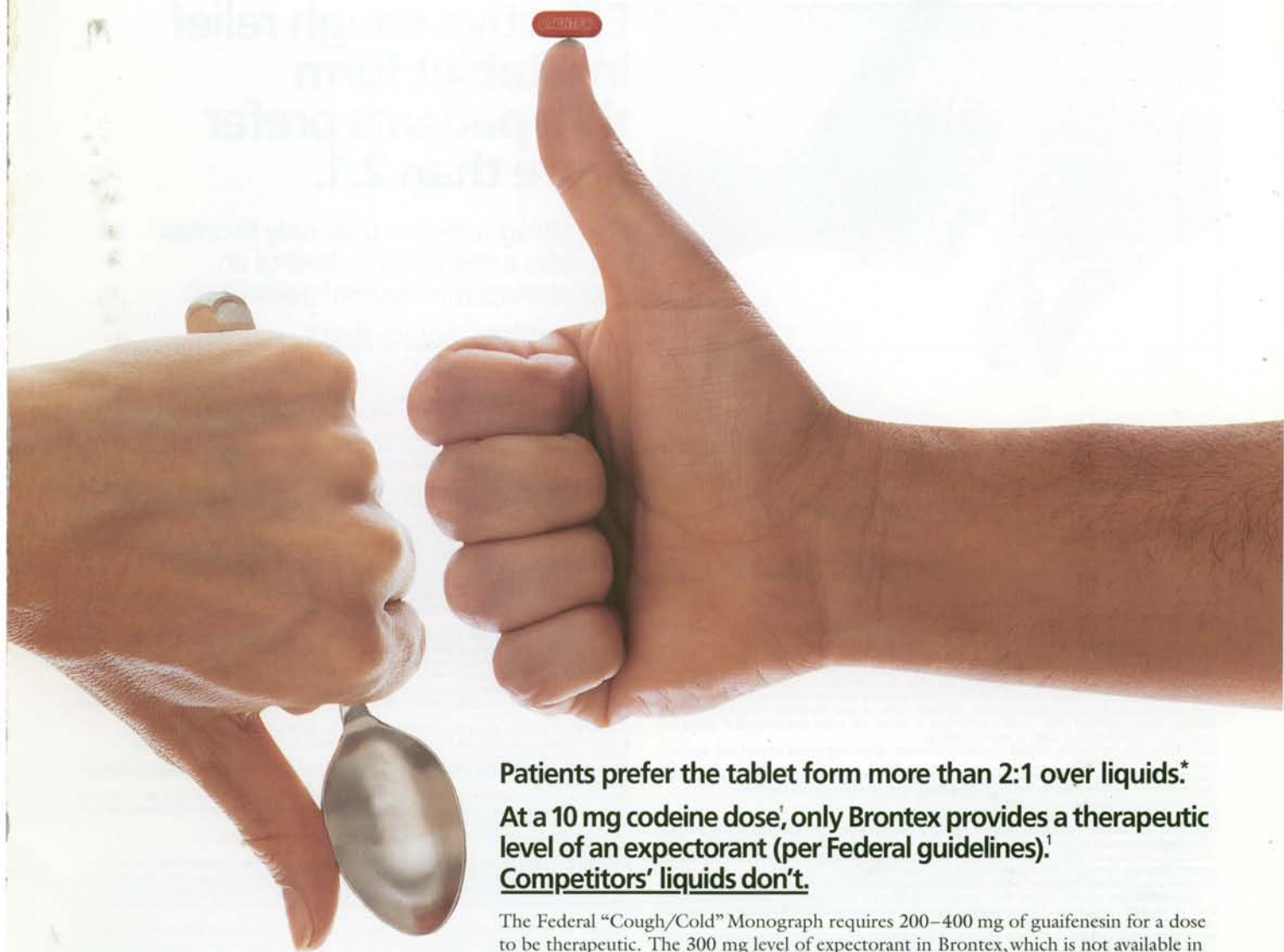
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Patients prefer cough tablets, and so will you when you see the unique Brontex® formula.



Patients prefer the tablet form more than 2:1 over liquids.*

At a 10 mg codeine dose[†], only Brontex provides a therapeutic level of an expectorant (per Federal guidelines)[†].

Competitors' liquids don't.

The Federal "Cough/Cold" Monograph requires 200–400 mg of guaifenesin for a dose to be therapeutic. The 300 mg level of expectorant in Brontex, which is not available in a teaspoon of any codeine cough liquid likely due to taste and solubility limitations, is made possible by the unique tablet form. And, since the tablet form is patient-preferred, Brontex not only has the formula for you, but the form for your patients as well.

FROM THE MAKERS OF ENTEX® PRODUCTS

Brontex®

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

GUAIFENESIN.....300mg



RIGHT FORM. RIGHT FORMULA.

Because Brontex contains codeine, some patients may experience dizziness, sedation, nausea, emesis, and constipation. Please see brief summary of prescribing information on next page.

* In a recent survey among 100 cough sufferers who took Brontex tablets and a prescription cough liquid in the past 12 months. Survey conducted via geographically-dispersed pharmacies. 71% of patients expressed a preference for the tablet form, 24% of patients expressed a preference for liquid form, and 5% of patients expressed no preference for either form. Data on file.

† The most commonly prescribed dose of most codeine/guaifenesin products is 1 teaspoon (1994 NIDDI data). Recommended adult dosage for most codeine/guaifenesin products is 2 teaspoons every 4 hours.

1 Tablet
Every
4 Hours

Brontex®

CODEINE PHOSPHATE...10mg

(Warning: May be habit forming)

GUAIFENESIN.....300mg



RIGHT FORM. RIGHT FORMULA.



Effective cough relief in a tablet form that patients prefer more than 2:1.

At a 10 mg codeine dose, only Brontex provides a therapeutic level of an expectorant (per Federal guidelines).

Competitors' liquids don't.

References:

1. Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Expectorant Drug Products for Over-the-Counter Human Use; Final Monograph, Final Rule. *Federal Register*, Vol. 54, No. 38, Tuesday, February 28, 1989.

Please see brief summary of prescribing information below.

Brontex®

(codeine phosphate/guaifenesin) tablets

DESCRIPTION: Each Brontex® tablet and 4 teaspoonfuls (20 mL) of Brontex liquid contains codeine phosphate.....10 mg

Warning — May be habit forming

guaifenesin.....300 mg

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

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

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

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

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

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

Hypotensive Effects: Codeine may produce hypotension in ambulatory patients.

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

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

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

The concomitant use of alcohol or other central nervous system depressants, including opiate agonists, sedatives, hypnotics, and tranquilizers, may have an additive effect and should be avoided or their dosage reduced. Codeine, like other opiate agonists, may produce orthostatic hypotension in some ambulatory patients. Patients should be cautioned accordingly.

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

Drug/Laboratory Test Interactions: Guaifenesin has been reported to interfere with clinical laboratory determinations of urinary 5-hydroxyindoleacetic acid (5-HIAA) and urinary vanillylmandelic acid (VMA). Because opiate agonists may increase biliary tract pressure, with resultant increases in plasma amylase or lipase levels, determination of these enzyme levels may be unreliable for 24 hours after an opiate agonist has been given.

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

Pregnancy:

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

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

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

Brontex® (codeine phosphate/guaifenesin) tablets

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

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

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

ADVERSE REACTIONS:

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

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

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

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

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

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

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

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

OVERDOSAGE:

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

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

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

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

DOSSAGE AND ADMINISTRATION:

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

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

Liquid: Adults and pediatric patients 12 years of age and older: 4 teaspoonfuls every 4 hours. **Pediatric patients 6 to under 12 years of age:** 2 teaspoonfuls every 4 hours.

HOW SUPPLIED:

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

NDC 0149-0440-01 bottle of 100.

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

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

CAUTION: Federal law prohibits dispensing without prescription.

Procter & Gamble Pharmaceuticals

Cincinnati, Ohio 45202

May 1995

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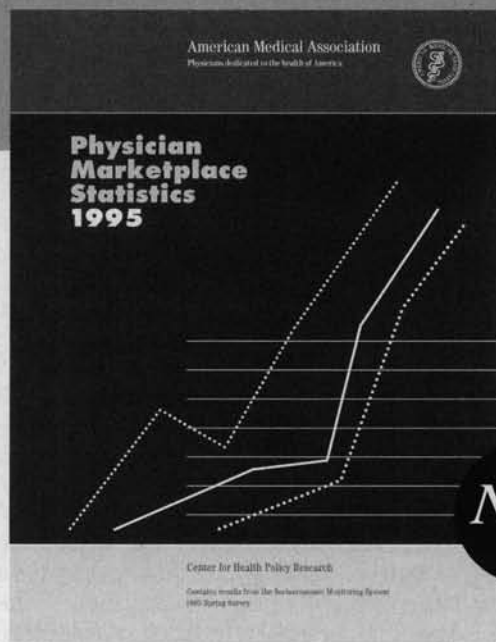
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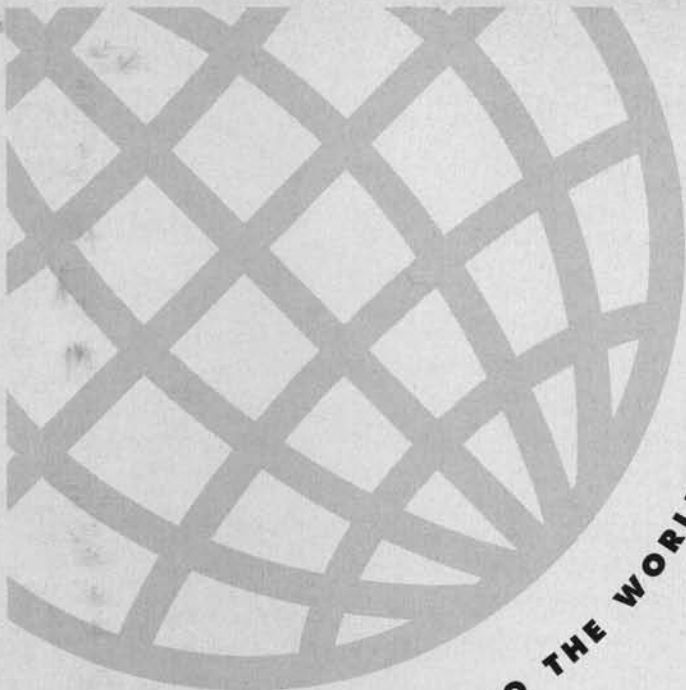
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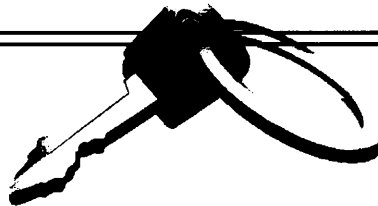
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1. Petersen P, Boysen G, Godtfredsen J, et al. Placebo-controlled, randomized trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: the Copenhagen AFASAK Study. *Lancet*. 1989;1:175-179.
2. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *N Engl J Med*. 1990;323:1505-1511.
3. Stroke Prevention in Atrial Fibrillation Investigators. Stroke Prevention in Atrial Fibrillation Study: final results. *Circulation*. 1991;84:527-539.
4. Connolly SJ, Laupacis A, Gent M, et al. Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. *J Am Coll Cardiol*. 1991;18:349-355.
5. Ezekowitz EM, Bridgers SL, James KE, et al. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. *N Engl J Med*. 1992;327:1406-1412.
6. Laupacis A, Albers G, Dunn M, et al. Antithrombotic therapy in atrial fibrillation. *Chest*. 1992;102(suppl 4):426S-433S.
7. Starkey I, Warlow C. Controversies in neurology: the secondary prevention of stroke in patients with atrial fibrillation. *Arch Neurol*. 1986;43:66-68.
8. Sherman DG, Hart RG, Easton JD. The secondary prevention of stroke in patients with atrial fibrillation. *Arch Neurol*. 1986;43:68-70.
9. Hachinski V. Atrial fibrillation and recurrent stroke. *Arch Neurol*. 1986;43:70.
10. Cook DJ, Guyatt DG, et al. Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest*. 1992;102(suppl 4):305S-311S.
11. Furberg CD, Psaty BM, Manolio TA, et al. Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). *Am J Cardiol*. 1994;74:236-241.
12. The European Atrial Fibrillation Trial Study Group. Optimal oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and recent cerebral ischemia. *N Engl J Med*. 1995;333:5-10.
13. Finn SD. Aiming for safe anticoagulation. *N Engl J Med*. 1995;333:54-55.
14. Lackner TE, Battis GN. Use of warfarin for nonvalvular atrial fibrillation in nursing home patients. *Arch Fam Med*. 1995;4:1017-1026.
15. Tinetti ME. Factors associated with serious injury during falls by ambulatory nursing home residents. *J Am Geriatr Soc*. 1987;35:644-648.
16. Volicer L, Rheaume Y, Brown J, et al. Hospice approach to the treatment of patients with advance dementia of the Alzheimer type. *JAMA*. 1986;256:2210-2213.
17. Wetle T. Age as a risk factor for inadequate treatment. *JAMA*. 1987;258:516.
18. Gurwitz JH, Avorn J, Ross-Degnan D, et al. Aging and the anticoagulant response to warfarin therapy. *Ann Intern Med*. 1992;116:901-904.
19. Avorn J. Benefit and cost analysis in geriatric care: turning age discrimination into health policy. *N Engl J Med*. 1984;310:1294-1301.
20. Beers MH, Ouslander JG, Fingold SF, et al. Inappropriate medication prescribing in skilled-nursing facilities. *Ann Intern Med*. 1992;117:684-689.

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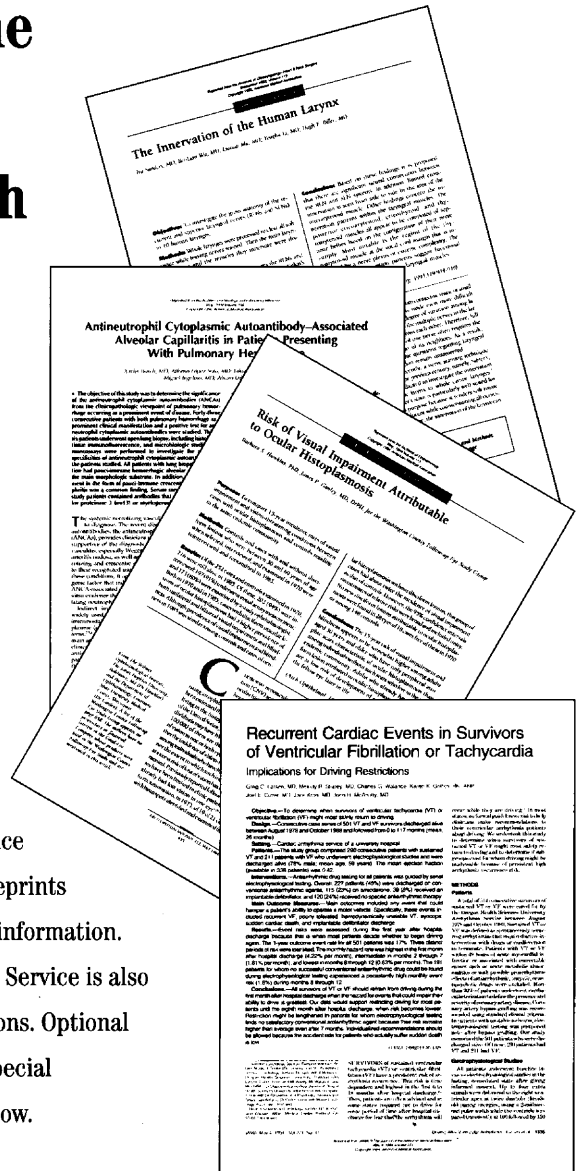
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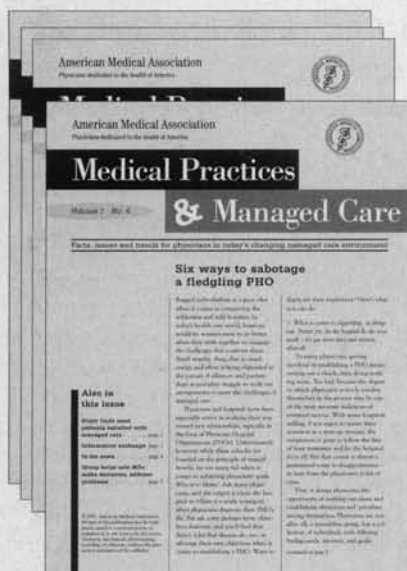
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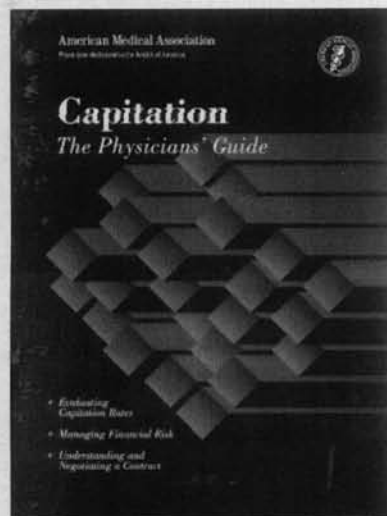
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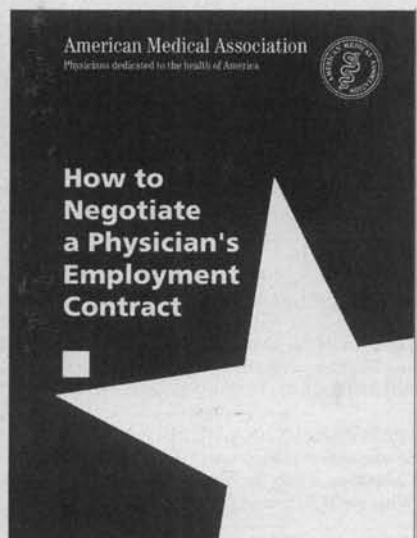
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Brief Summary of
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CARDIZEM[®] CD (diltiazem HCl) Capsules

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

- 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 diltiazem.
- 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.
- Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
- 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 concomi-

tantly 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. (See WARNINGS.)

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 recom-

mended 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, 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: Pefechiae, photosensitivity, pruritus, urticaria
Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarthral pain, polyuria, sexual difficulties

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, erythema multiforme, exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well-documented cases of generalized rash, characterized as leukocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and CARDIZEM therapy is yet to be established.

Prescribing Information as of January 1995

Marion Merrell Dow Inc.
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ccdb0195c

References: 1. Food and Drug Administration. *Approved Drug Products With Therapeutic Equivalence Evaluations* (Orange Book), US Dept of Health and Human Services. 14th ed. Washington, DC; 1994. 2. Cardizem CD prescribing information 3. Data on file, Marion Merrell Dow Inc.



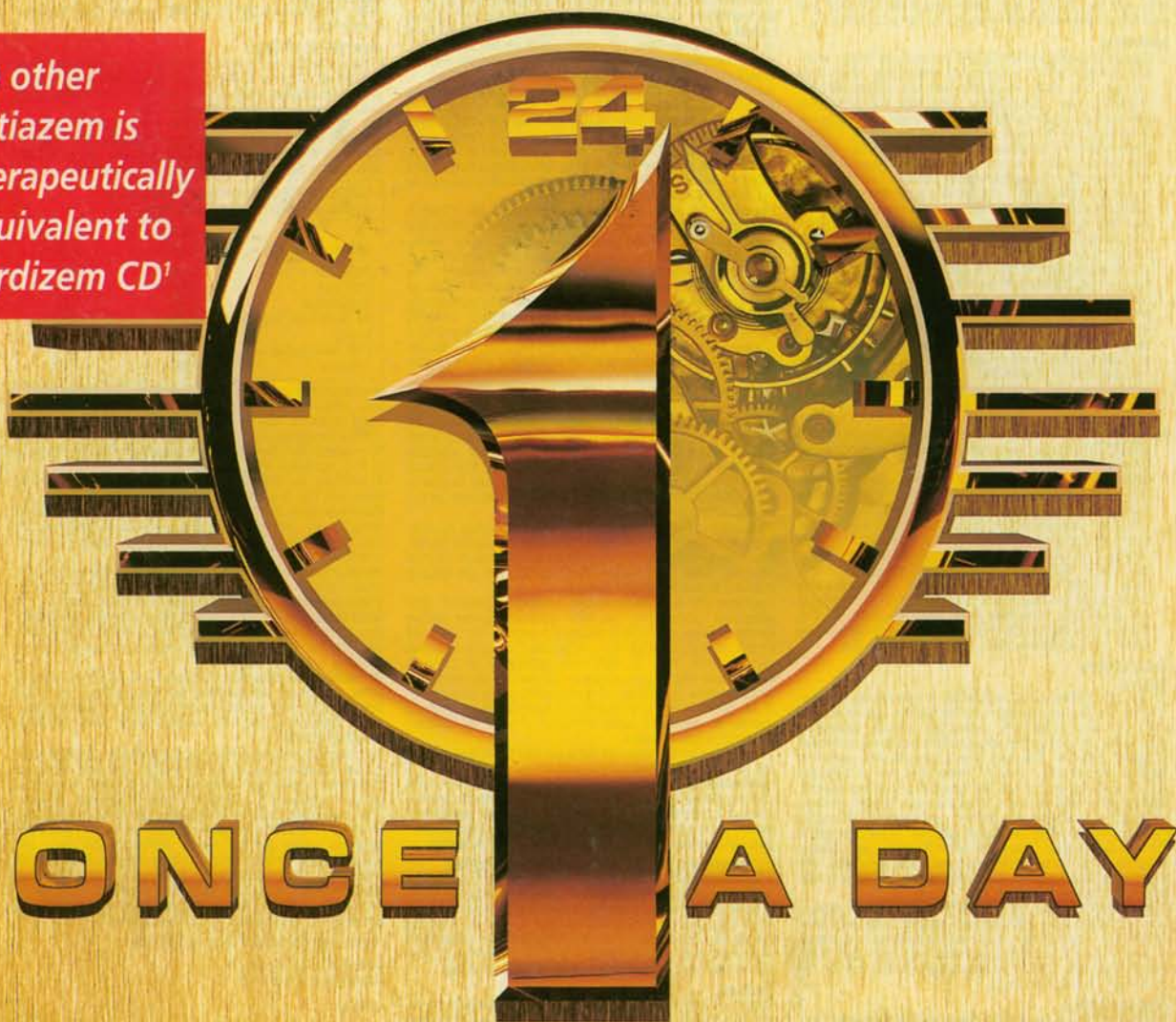
IN HYPERTENSION OR ANGINA

CARDIZEM[®] CD

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

**FOR EFFECTIVE
24-HOUR CONTROL**

No other
diltiazem is
therapeutically
equivalent to
Cardizem CD¹



ONCE A DAY

**A unique hemodynamic and safety profile
for hypertension or angina^{2,3}**

- A side-effect discontinuation rate comparable to placebo in both hypertension and angina trials³
- Most commonly reported side effects are headache (5.4%), bradycardia (3.3%), first-degree AV block (3.3%), dizziness (3.0%), edema (2.6%), ECG abnormality (1.6%), and asthenia (1.8%)²

Please see brief summary of prescribing information on adjacent page.