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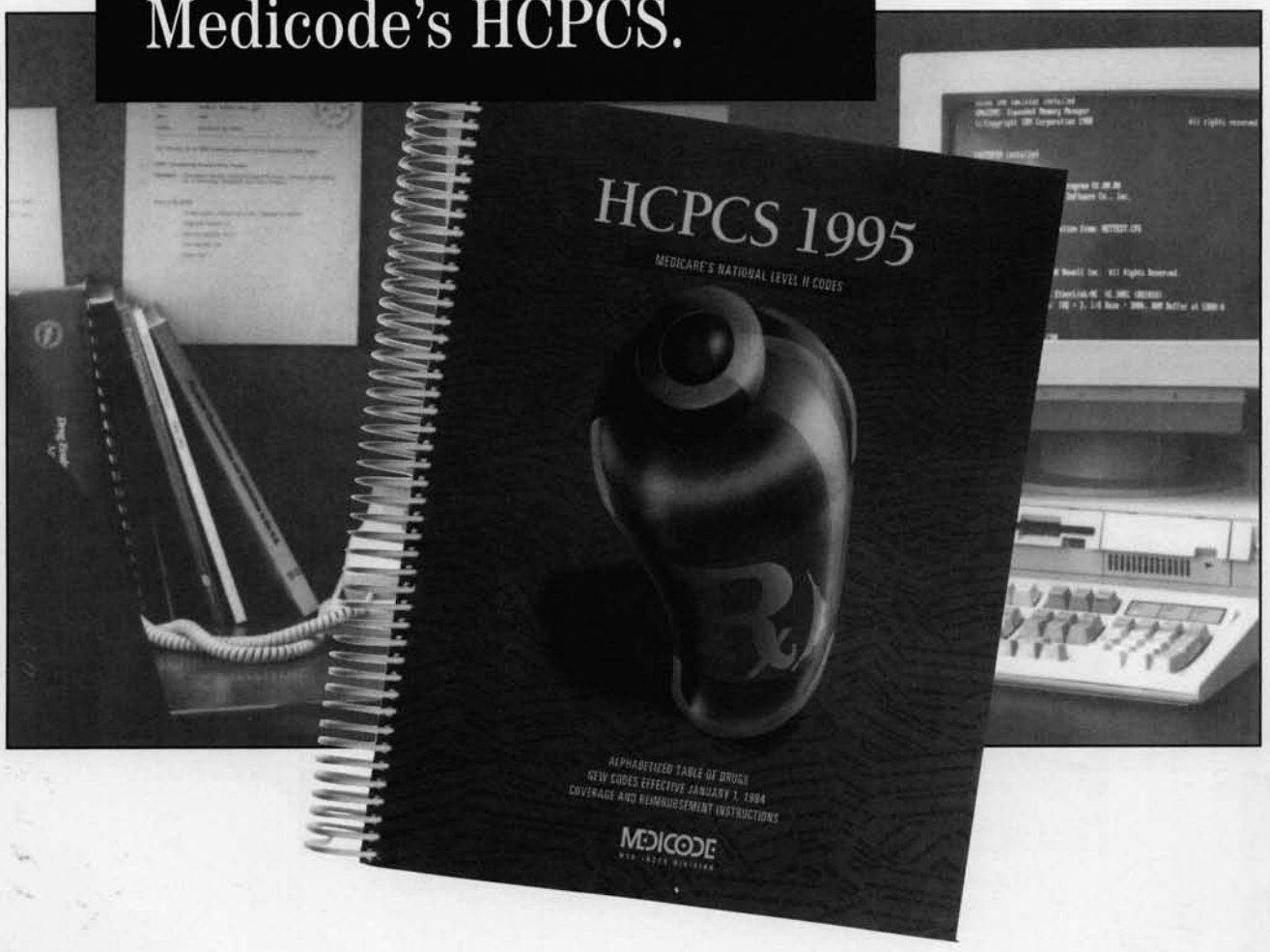

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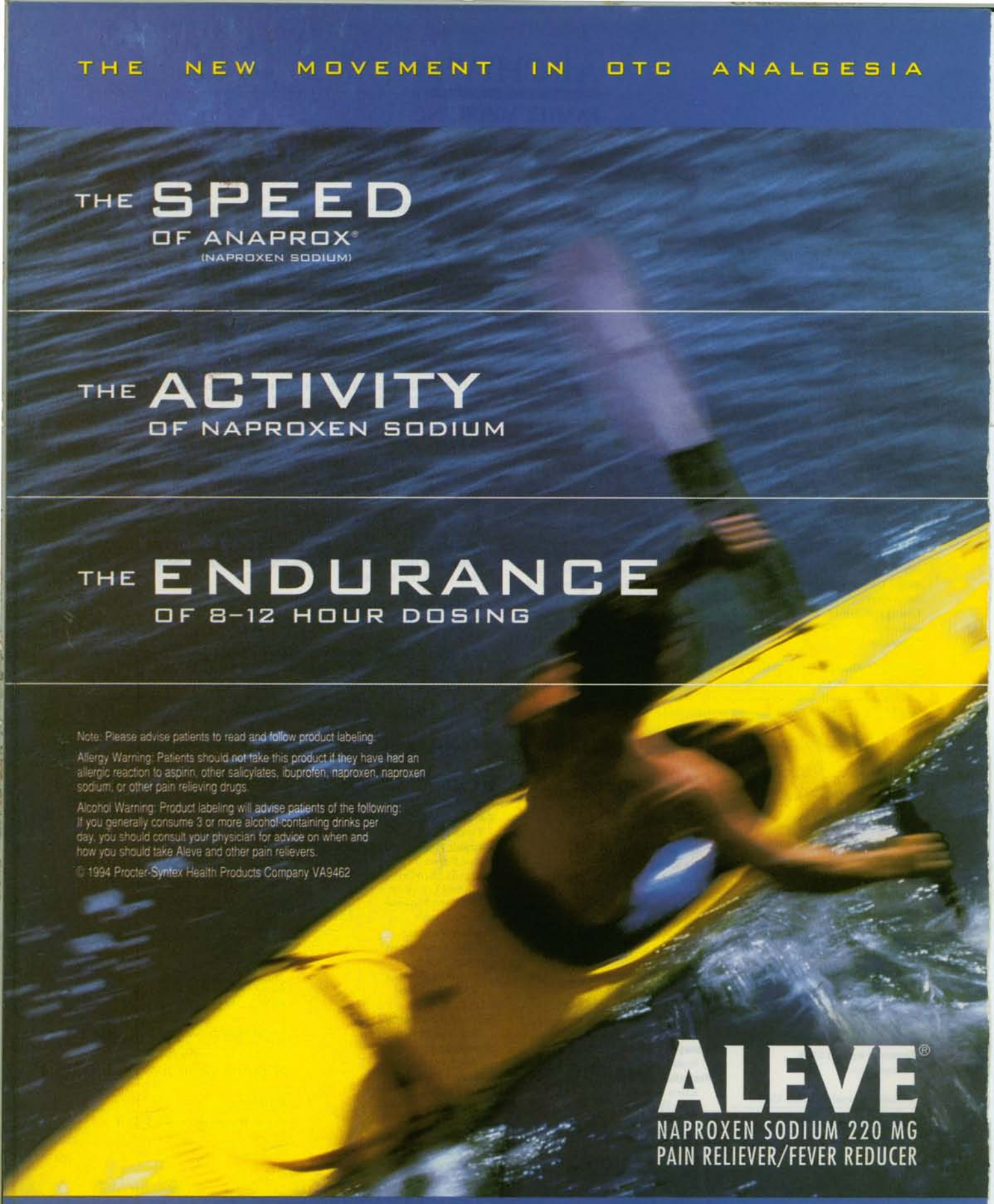

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ARCHIVES OF FAMILY MEDICINE

VOL 4 NO. 1, JANUARY 1995

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hemoglobin was significantly associated with mortality from diabetes (HR, 1.32; 95% CI, 1.21 to 1.43), ischemic heart disease (HR, 1.10; 95% CI, 1.04 to 1.17), and stroke (HR, 1.17; 95% CI, 1.05 to 1.30), but not cancer (HR, 0.99; 95% CI, 0.88 to 1.10). Results for any mention of specific causes of death were similar.
Conclusion: These results suggest possible benefit to the control of glycemia with respect to death due to vascular disease and diabetes.

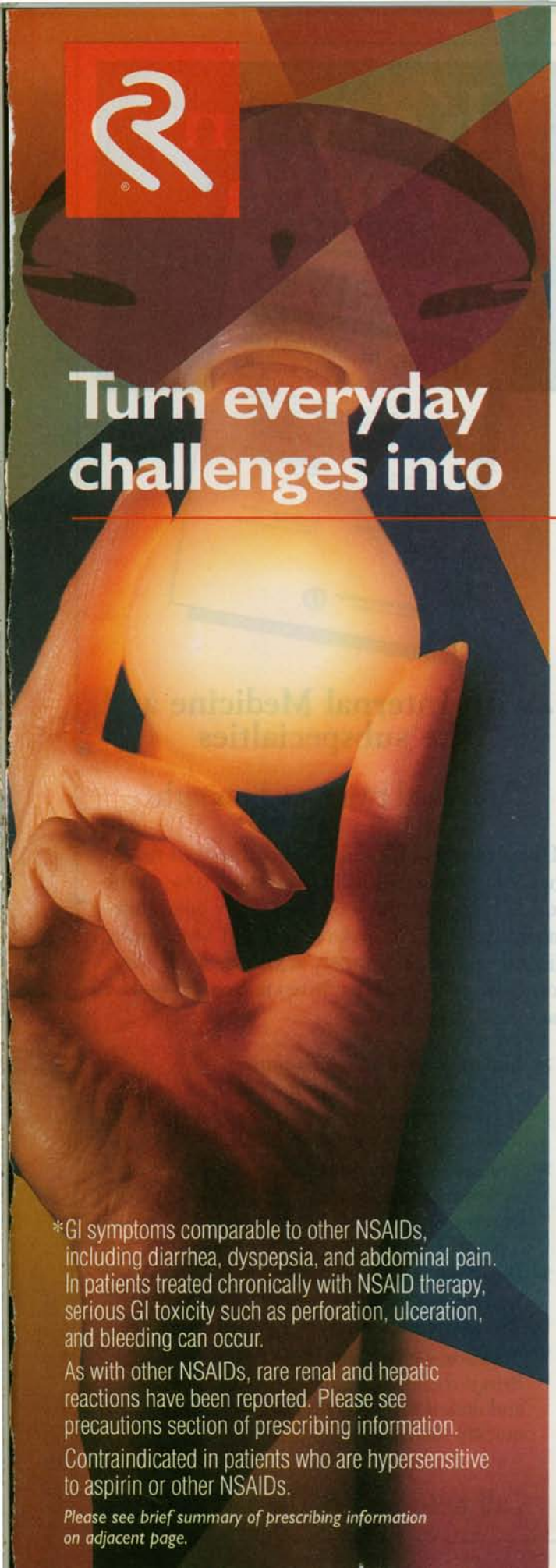
(1994;154:2473-2479) Scot E. Moss, MA, et al. Reprint requests to Ronald Klein, MD, Department of Ophthalmology and Visual Sciences, University of Wisonsin–Madison, 600 Highland Ave, F4/336 CSC, Madison, WI 53792-3220.

ARCHIVES OF NEUROLOGY

Pregnancy and Multiple Sclerosis: A Prospective Study

Objective: To conduct a prospective assessment of pregnancy on women with multiple sclerosis (MS), focusing on pregnancy outcome and relapses during gestation and up to 6 months after delivery.
Design: Expected numbers of relapses were based on data for (1) "self-controls": the mothers ("cases") themselves prior to becoming pregnant and (2) "matched controls": female patients with MS "matched" to the mothers for year of birth, age of MS onset, MS type, MS course, and initial MS symptom(s).
Setting: Cases and controls were identified from an ambulatory care MS clinic that serves the province of British Columbia, Canada.
Patients or Other Participants: Women with a diagnosis of MS who attended the MS clinic during 1982 through 1986 and subsequently became pregnant during 1982 through 1989 inclusive were included in the study as cases. Matched controls were women with MS who attended the MS clinic during the same period but did not become pregnant.
Results: No significant increase in relapse rate was found for cases during the first two trimesters of gestation. The number of relapses was significantly less than expected during the third trimester compared with matched controls (χ^2=6.80, df=1, P<.02), but not compared with self-controls (χ^2=3.39, df=1, P>.05). The observed number of relapses for the 6 months after delivery did not differ significantly from expected (self-controls: χ^2=2.84, df=2, P>.05; matched controls: χ^2=1.76, df=2, P>.05).
Conclusion: These data suggest that neither pregnancy nor the 6-month period after delivery is a risk factor for relapse in MS. They are consistent with previous observations that, in the long term, pregnancy does not influence subsequent MS disability.

(1994;51:1120-1124) A. Dezza Sadovnick, PhD, et al, Department of Medical Genetics, University of British Columbia, Room 226, 6174 University Blvd, Vancouver, British Columbia, Canada V6T 1Z3.



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*GI symptoms comparable to other NSAIDs, including diarrhea, dyspepsia, and abdominal pain. In patients treated chronically with NSAID therapy, serious GI toxicity such as perforation, ulceration, and bleeding can occur.

As with other NSAIDs, rare renal and hepatic reactions have been reported. Please see precautions section of prescribing information.

Contraindicated in patients who are hypersensitive to aspirin or other NSAIDs.

Please see brief summary of prescribing information on adjacent page.

Effective relief with a low incidence of peptic ulcer*

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But you faced fatality. And felt
relief: you'd earned at last an
honorable discharge from your
losing side; had no more need for
a point to it all.

Still, from shame, you cloaked
your thankfulness; feigned
the good fight, shammed your
compliance with our pills
(care's give-and-take conspiracy).

Amid secret tastings of deathday
as birthday, you scraped a last laurel
for your sidelined life by
dousing all your years' candles
with your final blow.

John Graham-Pole, MD, MRCP
University of Florida
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Unlike other codeine brands, new Brontex, with its convenient dosing regimen, reaches well into the daily therapeutic range for guaifenesin (1,200 mg to 2,400 mg) set by federal guidelines.

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

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

FEWER COUGHS, WETTER COUGHS

Please see brief summary of prescribing information on next page.

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Cough relief designed to make remaining coughs more productive

Up to 3 times more guaifenesin than other codeine brands

Exceeds the minimum therapeutic requirements for guaifenesin set by federal guidelines

FEWER COUGHS, WETTER COUGHS

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

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

Brontex®

(codeine phosphate/guaifenesin) tablets

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

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

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

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

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

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

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

Codeine may cause or aggravate constipation.

Hypotensive Effects: Codeine may produce hypotension in ambulatory patients.

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

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

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

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

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

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

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

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

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

Pregnancy:

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

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

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

Brontex® (codeine phosphate/guaifenesin) tablets

signs usually disappear during the first few days of life.

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

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

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

ADVERSE REACTIONS:

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

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

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

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

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

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

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

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

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

OVERDOSAGE:

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

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

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

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

DOSAGE AND ADMINISTRATION:

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

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

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

HOW SUPPLIED:

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

NDC 0149-0440-01 bottle of 100.

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

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

CAUTION: Federal law prohibits dispensing without prescription.

Procter & Gamble Pharmaceuticals
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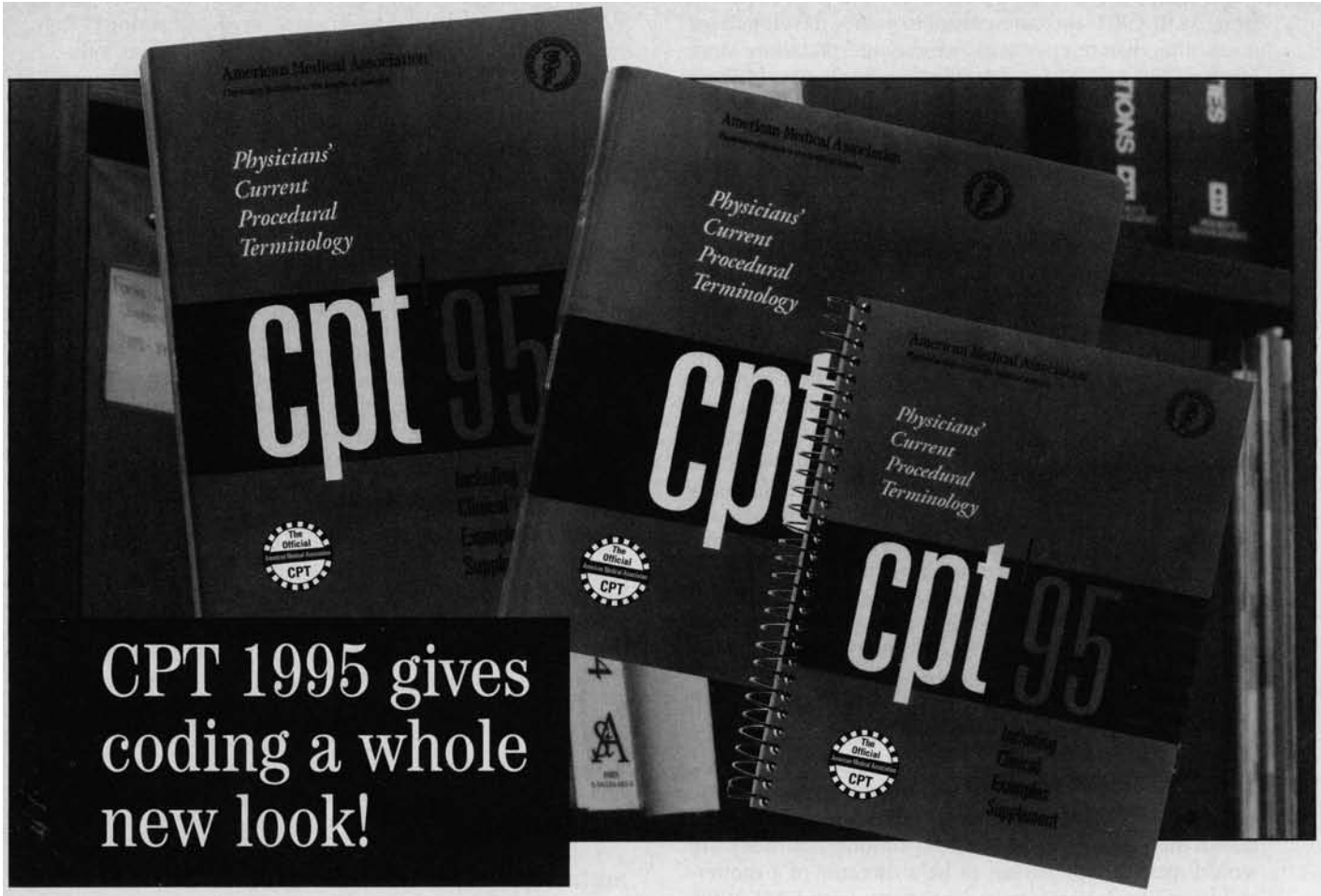

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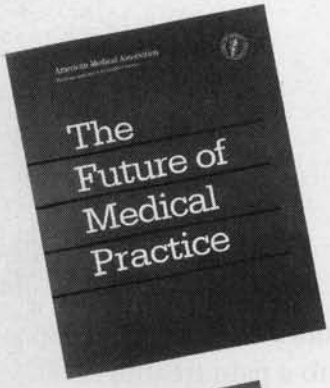

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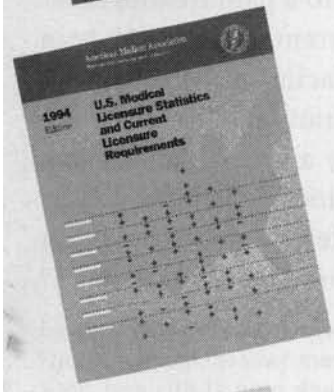
Order #: OP211594NT. AMA member price: $35.00. Nonmember price: $49.00.



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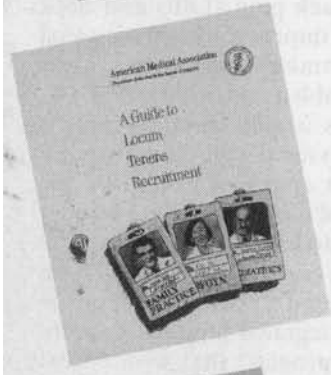
ISBN 0-89970-544-8. 85 pages, 30 tables, softbound. Publication date: 1994; annual.
Order #: OP399094NT. AMA member price: $50.00. Nonmember price: $75.00.



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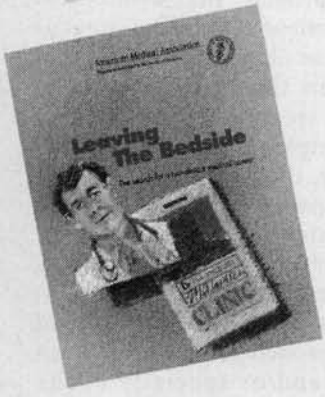
AMA member price: $20.00. Nonmember price: $25.00.



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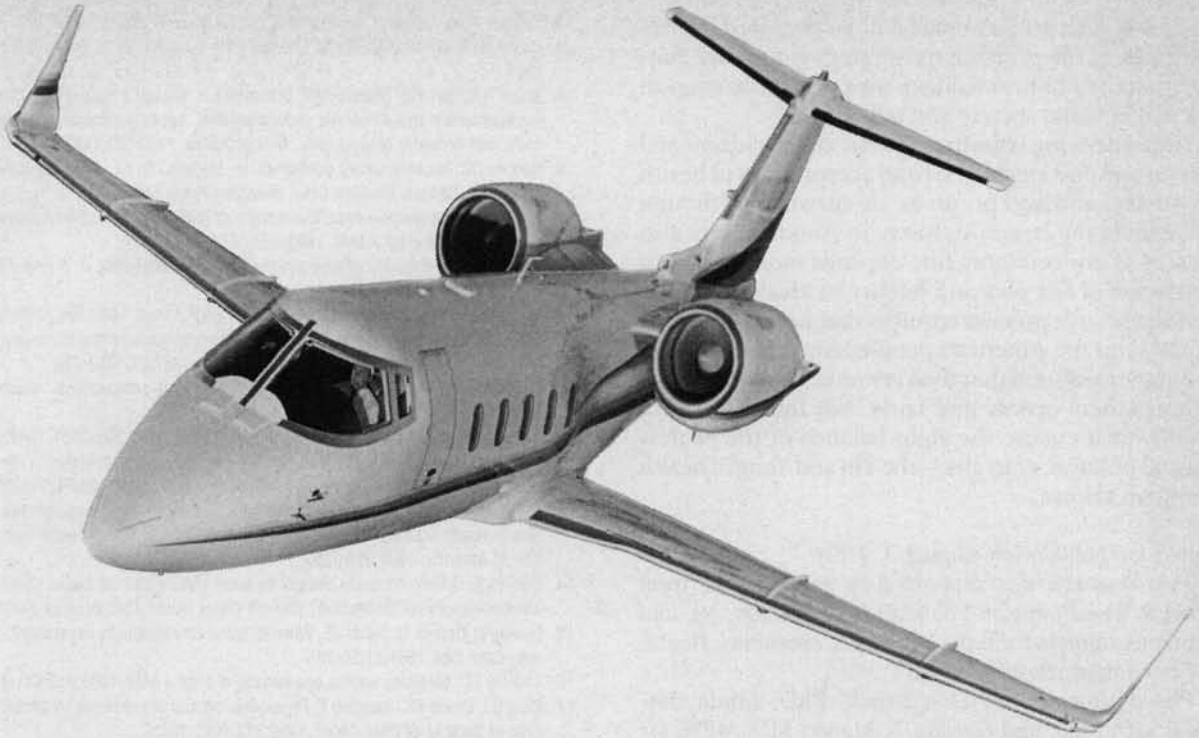

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(diltiazem HCl) 120-, 180-, 240-, 300-mg Capsules

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Brief Summary of
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CARDIZEM® CD
(diltiazem HCl)
Capsules

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

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

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

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

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

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

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

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

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

CARDIZEM CD Capsule Placebo-Controlled Angina and Hypertension Trials Combined

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

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

Prescribing Information as of April 1993

Marion Merrell Dow Inc.
Kansas City, MO 64114

ccdb0493a

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

MARION MERRELL DOW INC.
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KANSAS CITY, MO 64114

IN HYPERTENSION OR ANGINA

CARDIZEM® CD

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

FOR EFFECTIVE 24-HOUR CONTROL

ONCE A DAY

A unique hemodynamic and safety profile for hypertension or angina[1,2]

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

Please see brief summary of prescribing information on adjacent page.