Cardizem SR advertisement.

[s.l.]: [s.n.], 1988

HELPING TO ACHIEVE THE FOUR GOALS[1] OF ANTIHYPERTENSIVE THERAPY

NEW

CARDIZEM® SR

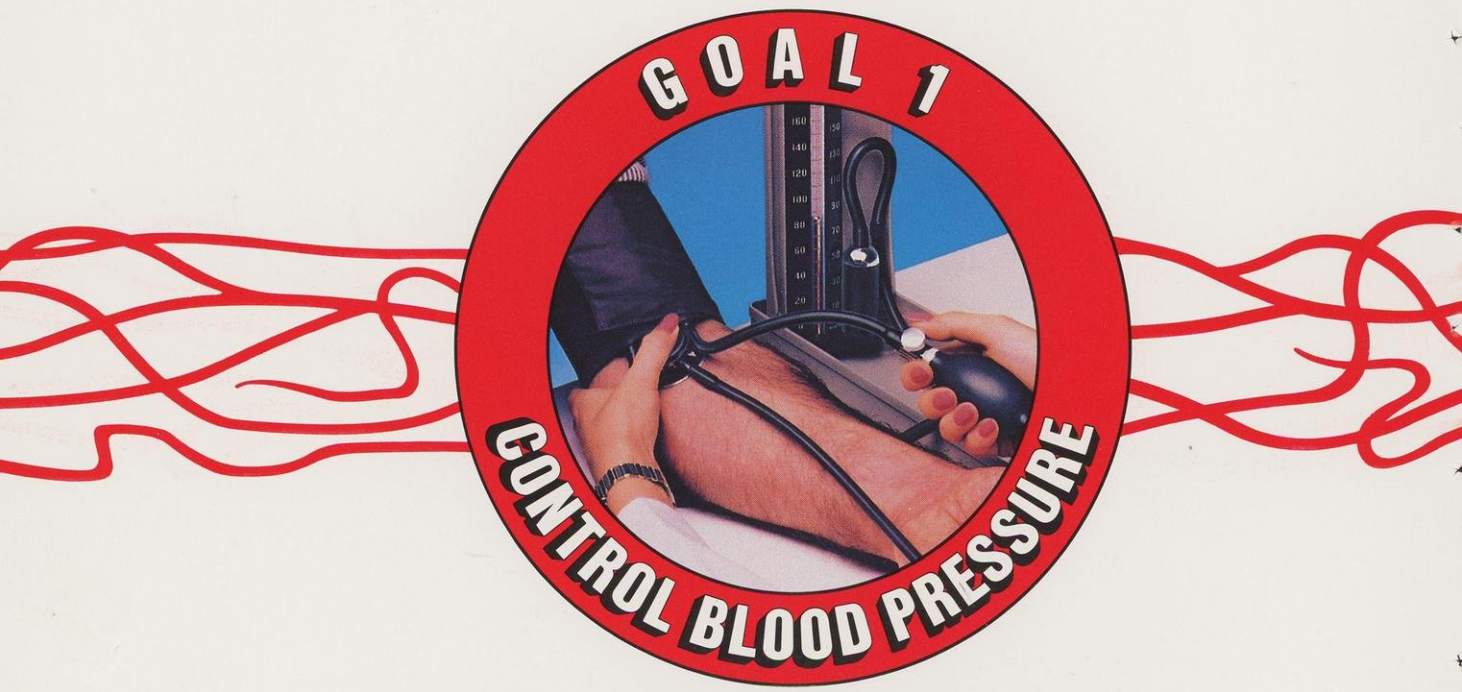
(diltiazem HCl) sustained release capsules

For hypertension

90 mg SR bid

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

ACHIEVES BLOOD PRESSURE REDUCTION PLUS HIGH PATIENT ACCEPTANCE



EFFECTIVE MONOTHERAPY

Lowers total peripheral resistance[2]

Effectively controls blood pressure, comparable to beta-blockers and diuretics[3-5]

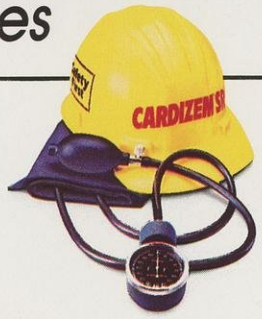
Is effective as monotherapy in mild to moderate hypertension, in short- and longer-term clinical trials[6-8]

NEW

CARDIZEM® SR

(diltiazem HCl) sustained release capsules

For hypertension



A LOW SIDE-EFFECT PROFILE*

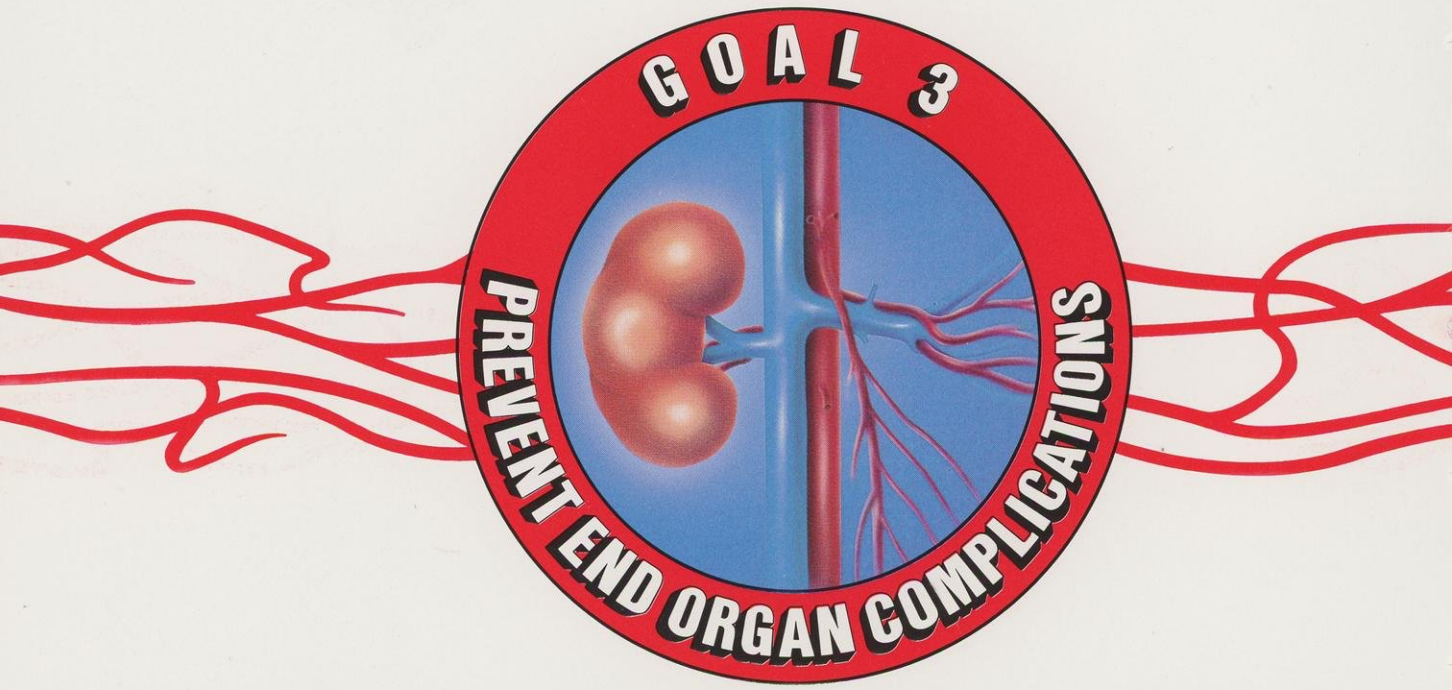
Is rarely associated with side effects that slow patients down or impair performance—fatigue, drowsiness, depression, constipation, sexual dysfunction, or postural hypotension[3-5,8]

Maintains or improves exercise performance, for greater feeling of well-being[6,9]

*Please see Adverse Reactions section of brief summary of prescribing information on last page of this advertisement.

90 mg SR bid

HELPS ACHIEVE ADDITIONAL EFFECTS WHICH ENHANCE ANTIHYPERTENSIVE THERAPY



AVOIDS TARGET ORGAN COMPLICATIONS

Lowers total vascular resistance, with enhanced blood flow to key target organs, including the kidney and heart[7,10]

Lowers renal vascular resistance, and causes no disturbance of fluid or electrolyte balance[7,11]

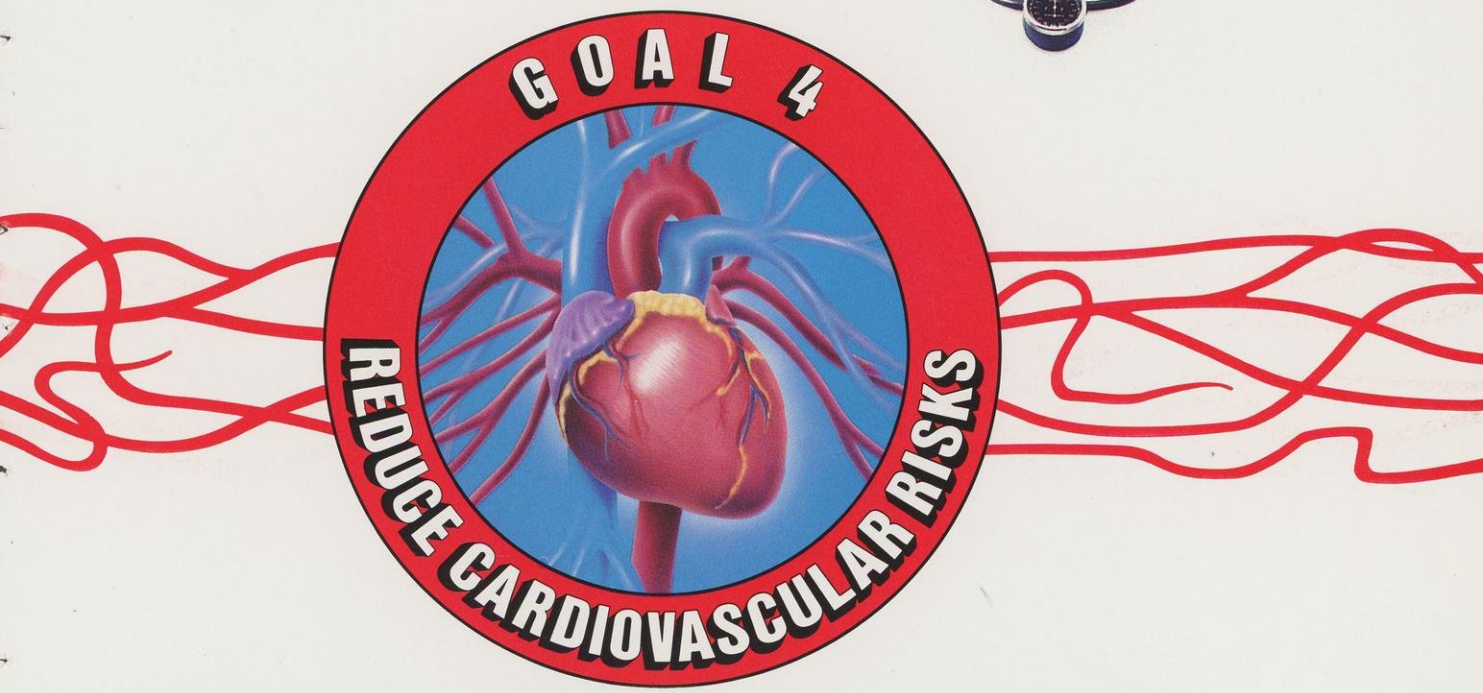
Reduces left ventricular hypertrophy, a common cardiac abnormality in hypertension[7,12]

NEW

CARDIZEM® SR

(diltiazem HCl) sustained release capsules

For hypertension



BENEFICIAL CARDIOVASCULAR EFFECTS

Does not adversely affect serum lipid levels, important in the development of atherosclerosis[3,6,13]

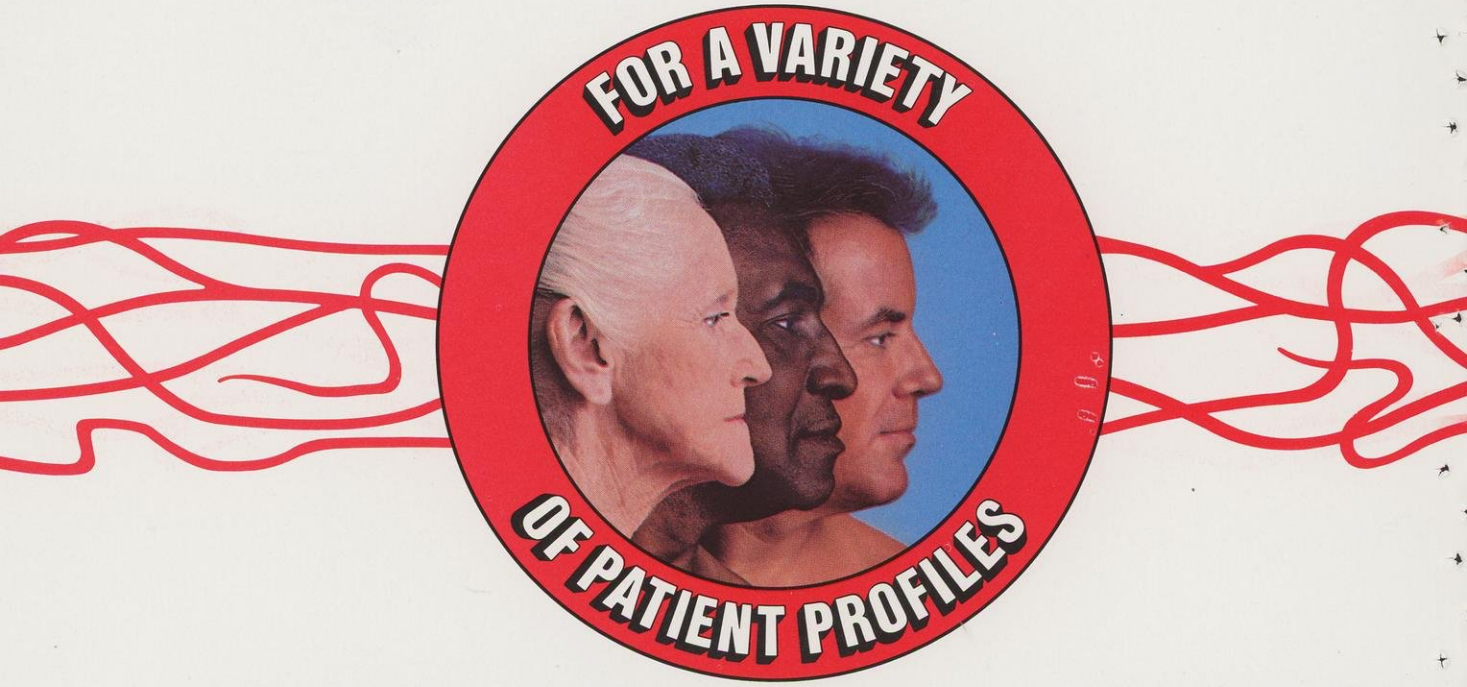
Controls hypertension, a major risk factor for stroke and heart disease[10]

Decreases cardiac work load as it increases myocardial oxygen supply[10,13]

90 mg SR bid

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

HELPS ACHIEVE THE FOUR GOALS IN A WIDE RANGE OF HYPERTENSIVE PATIENTS



FOR OLDER, BLACK, AND ACTIVE PATIENTS

Works as well as diuretics in older and black patients — without the metabolic or hemodynamic disturbances of the diuretics[5,14]

As effective as beta-blockers with fewer side effects[3,4]* — often a better choice for younger, active patients as well as patients with certain coexisting conditions*: COPD, asthma, peripheral vascular disease, coronary artery disease, depression, and hyperlipidemia[4,12,13,15]

*Please see Adverse Reactions and Contraindications sections of brief summary of prescribing information on last page of this advertisement.

NEW

CARDIZEM® SR

(diltiazem HCl) sustained release capsules

For hypertension

A SIMPLIFIED PRESCRIBING REGIMEN

Start with Cardizem SR 90 mg bid in your newly diagnosed patient**

Add Cardizem SR for an enhanced antihypertensive effect when your patient is inadequately controlled by another agent†

Switch to Cardizem SR when your patient is experiencing side effects or is not responding to another regimen

**Dosage must be adjusted to each patient's needs, starting with 60 to 120 mg twice daily.

†Dosage may need to be adjusted when adding one antihypertensive agent to another.

Please see brief summary of prescribing information on next page.

0928A9

NEW

CARDIZEM® SR

(diltiazem HCl) sustained release capsules

For hypertension

HELPING TO ACHIEVE THE FOUR GOALS OF ANTIHYPERTENSIVE THERAPY

Starting Dosage:

90 mg bid*

Also Available: 120-mg capsules

*Dosage must be adjusted to each patient's needs, starting with 60 to 120 mg twice daily.

BRIEF SUMMARY
CARDIZEM® SR
(diltiazem hydrochloride)
Sustained Release 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 (nine of 2,111 patients or 0.43%). 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). 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 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 Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any 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. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis 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%. 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 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

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 some reduction in early individual pup weights and survival rates. 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 adverse events described below represent events observed in clinical studies of hypertensive patients receiving either CARDIZEM Tablets or CARDIZEM SR Capsules as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and 1° AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related. The most common events observed in clinical studies (over 2,100 patients) of angina patients and hypertensive patients receiving CARDIZEM Tablets or CARDIZEM SR Capsules were (ie, greater than 1%) edema (5.4%), headache (4.5%), dizziness (3.4%), asthenia (2.8%), first-degree AV block (1.8%), flushing (1.7%), nausea (1.6%), bradycardia (1.5%), and rash (1.5%).

DOUBLE BLIND PLACEBO CONTROLLED HYPERTENSION TRIALS

Adverse	Diltiazem N=315 # pts (%)	Placebo N=211 # pts (%)
headache	38 (12%)	17 (8%)
AV block first degree	24 (7.6%)	4 (1.9%)
dizziness	22 (7%)	6 (2.8%)
edema	19 (6%)	2 (0.9%)
bradycardia	19 (6%)	3 (1.4%)
ECG abnormality	13 (4.1%)	3 (1.4%)
asthenia	10 (3.2%)	1 (0.5%)
constipation	5 (1.6%)	2 (0.9%)
dyspepsia	4 (1.3%)	1 (0.5%)
nausea	4 (1.3%)	2 (0.9%)
palpitations	4 (1.3%)	2 (0.9%)
polyuria	4 (1.3%)	2 (0.9%)
somnolence	4 (1.3%)	—
alk phos increase	3 (1%)	1 (0.5%)
hypotension	3 (1%)	1 (0.5%)
insomnia	3 (1%)	1 (0.5%)
rash	3 (1%)	1 (0.5%)
AV block second degree	2 (0.6%)	—

In addition, the following events were reported infrequently (less than 1%) or have been observed in angina trials. In many cases, the relation to drug is uncertain.

Cardiovascular: Angina, arrhythmia, bundle branch block, tachycardia, ventricular extrasystoles, congestive heart failure, syncope.

Nervous System: Amnesia, depression, gait abnormality, hallucinations, nervousness, paresthesia, personality change, tinnitus, tremor, abnormal dreams.

Gastrointestinal: Anorexia, diarrhea, dysgeusia, mild elevations of SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase, thirst.

Dermatological: Petechiae, pruritus, photosensitivity, urticaria.

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, sexual difficulties, nasal congestion, nocturia, osteoarticular pain, impotence, dry mouth.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. Definitive cause and effect relationship between these events and CARDIZEM therapy cannot yet be established.

Issued 1/89

References: **1.** Staessen J, Fagard R, Lignen P, et al: *Pract Cardiol* 1986;12(5):55-65. **2.** Safar ME, Simon AC, Levenson JA, et al: *Circ Res* 1983;52(suppl I):169-173. **3.** Massie B, MacCarthy EP, Ramanathan KB, et al: *Ann Intern Med* 1987;107(2):150-157. **4.** Weir MR, Josselson J, Giard MJ, et al: *Am J Cardiol* 1987;60:36I-41I. **5.** Frishman WH, Zawada ET Jr, Smith LK, et al: *Am J Cardiol* 1987;59:615-623. **6.** Pool PE, Seagren SC, Salel AF: *Am J Cardiol* 1985;56:86H-91H. **7.** Amodeo C, Kobrin I, Ventura HO, et al: *Circulation* 1986;73(1):108-113. **8.** Pool PE, Seagren SC, Salel AF: *Cardiol Board Rev* 1986;3(10):77-91. **9.** Szlachcic J, Hirsch AT, Tubau JF, et al: *Am J Cardiol* 1987;59:393-399. **10.** O'Rourke RA: *Am J Cardiol* 1985;56:34H-40H. **11.** Sunderrajan S, Reams G, Bauer JH: *Hypertension* 1986;8:238-242. **12.** Massie BM, Hirsch AT, Inouye IK, et al: *Am J Med* 1984;77(4A):135-142. **13.** Schulte K-L, Meyer-Sabellek WA, Haertenberger A, et al: *Hypertension* 1986;8:859-865. **14.** Frishman WH, Kirkendall W, Lunn J, et al: *Am J Cardiol* 1985;56:92H-96H. **15.** Materson BJ: *Drug Ther* 1985;15(11):177-188.

Another patient benefit product from

PHARMACEUTICAL DIVISION
MARION LABORATORIES, INC.
KANSAS CITY, MO 64137

CSRAT695
0928A9

DOWN SAFE

CARDIZEM® SR
(diltiazem HCl) sustained release capsules

For hypertension

Hypertension control, not complaints

CSRAB976

Please see brief summary of prescribing information on back page.

6223H0

CARDIZEM® SR

(diltiazem HCl) sustained release capsules

For hypertension

LOWERS BLOOD PRESSURE SAFELY

Unsurpassed efficacy

Low side-effect profile

Convenient bid dosage

Please see brief summary of prescribing information on back page.


CARDIZEM SR
Hypertension control, not complaints

Rx Cardizem SR
90 mg
Sig:
Cap i bid

Dosage flexibility:

90 mg SR **120 mg SR**

CARDIZEM® SR

(diltiazem HCl) sustained release capsules

For hypertension

HYPERTENSION CONTROL, NOT COMPLAINTS

BRIEF SUMMARY
CARDIZEM® SR
(diltiazem hydrochloride)
Sustained Release Capsules
CONTRAINDICATIONS

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WARNINGS

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dyspepsia	4 (1.3%)	1 (0.5%)
nausea	4 (1.3%)	2 (0.9%)
palpitations	4 (1.3%)	2 (0.9%)
polyuria	4 (1.3%)	2 (0.9%)
somnolence	4 (1.3%)	—
alk phos increase	3 (1%)	1 (0.5%)
hypotension	3 (1%)	1 (0.5%)
insomnia	3 (1%)	1 (0.5%)
rash	3 (1%)	1 (0.5%)
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Nervous System: Amnesia, depression, gait abnormality, hallucinations, nervousness, paresthesia, personality change, tinnitus, tremor, abnormal dreams.
Gastrointestinal: Anorexia, diarrhea, dysgeusia, mild elevations of SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase, thirst.
Dermatological: Petechiae, pruritus, photosensitivity, urticaria.
Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, sexual difficulties, nasal congestion, nocturia, osteoarticular pain, impotence, dry mouth.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. Definitive cause and effect relationship between these events and CARDIZEM therapy cannot yet be established.

Issued 1/89

MARION MERRELL DOW INC.
PRESCRIPTION PRODUCTS DIVISION
KANSAS CITY, MO 64114

The benefit of antianginal protection plus safety...

CARDIZEM®: A FULLER LIFE

diltiazem HCl/Marion

- **A remarkable safety profile**[1-6]
  The low incidence of side effects with Cardizem allows patients to feel better.
- **Protection against angina attacks**[1,5,7-9]
  The predictable efficacy of Cardizem in stable exertional and vasospastic angina allows patients to do more.*
- **A decrease in myocardial oxygen demand**
  Resulting from a lowered heart rate-blood pressure product.[5]
- **Compatible with other antianginals**[6†]
- **Safe in angina with coexisting hypertension, COPD, asthma, or PVD**[1,3,5,6]

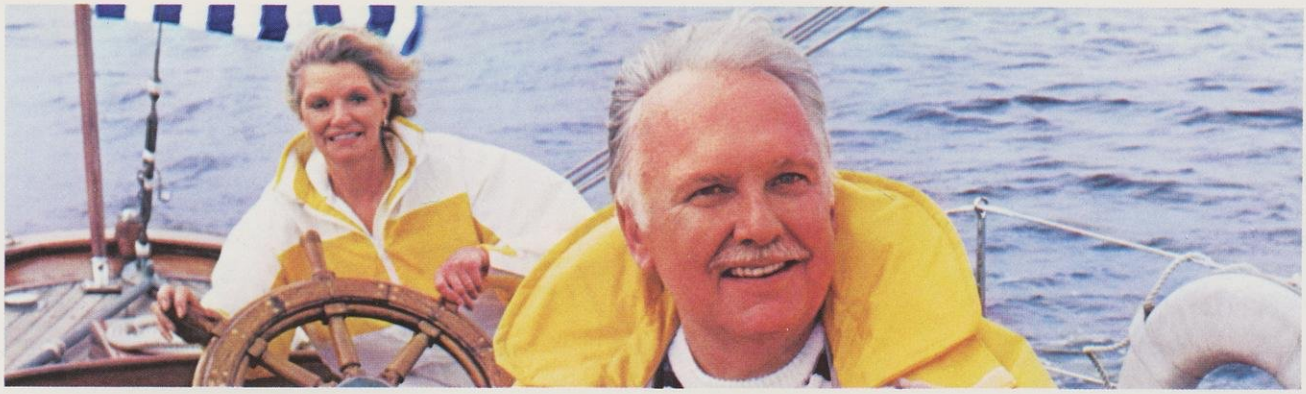
60 mg 90/120 mg GREATER DOSAGE FLEXIBILITY

**CARDIZEM® (diltiazem HCl) is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.*

†See Warnings and Precautions.

Please see brief summary of prescribing information on the next page.

1419H8



CARDIZEM® ANTIANGINAL PROTECTION PLUS SAFETY

diltiazem HCl/Marion

Usual maintenance dosage range: 180-360 mg/day

BRIEF SUMMARY
Professional Use Information

CARDIZEM®
(diltiazem HCl)
30 mg, 60 mg, 90 mg and 120 mg Tablets

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 (six of 1,243 patients for 0.48%). 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). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** 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 have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most 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 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 Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any 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. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly 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%. 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 one-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

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 some reduction in early individual pup weights and survival rates. 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.

Rx

Cardizem® (diltiazem HCl)

☐ 60 mg ☐ 90 mg
☐ 120 mg

Sig: tid

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	Angina, arrhythmia, AV block (first degree), AV block (second or third degree—see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope.
Nervous System:	Amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.
Gastrointestinal:	Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase.
Dermatologic:	Petechiae, pruritus, photosensitivity, urticaria.
Other:	Amblyopia, CPK elevation, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

Issued 3/1/88

See complete Professional Use Information before prescribing.

References: 1. Schroeder JS: Mod Med 1982;50(Sept):94-116. **2.** Cohn PF, Braunwald E: Chronic ischemic heart disease, in Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine, ed 2. Philadelphia, WB Saunders Co, 1984, chap 39. **3.** O'Rourke RA: Am J Cardiol 1985;56:34H-40H. **4.** McCall D, Walsh RA, Frohlich ED, et al: Curr Probl Cardiol 1985;10(8):6-80. **5.** Frishman WH, Charlap S, Goldberger J, et al: Am J Cardiol 1985;56:41H-46H. **6.** Shapiro W: Consultant 1984;24(Dec):150-159. **7.** O'Hara MJ, Khurmi NS, Bowles MJ, et al: Am J Cardiol 1984;54:477-481. **8.** Strauss WE, McIntyre KM, Parisi AF, et al: Am J Cardiol 1982; 49:560-566. **9.** Feldman RL, Pepine CJ, Whittle J, et al: Am J Cardiol 1982;49:554-559.

Another patient benefit product from

PHARMACEUTICAL DIVISION
MARION LABORATORIES, INC.
KANSAS CITY, MO 64137

1419H8

NEW FOR ANGINA

ONCE-A-DAY

CARDIZEM® CD

(diltiazem HCl)

CCDAJ165/A6603

Please see brief summary of prescribing information on an adjacent page.

1030R2

ONCE-A-DAY CARDIZEM® CD

(diltiazem HCl)

THE ONE FOR BOTH ANGINA AND HYPERTENSION

BRIEF SUMMARY

INDICATIONS AND USAGE

CARDIZEM CD is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive medications.

CARDIZEM CD is indicated for the management of chronic stable angina and angina due to coronary artery spasm.

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 3,290 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, and 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. Dosages of similarly metabolized drugs such as cyclosporin, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM 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 1,200 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.

Available as Once-A-Day

120-mg capsules

180-mg capsules

240-mg capsules

300-mg capsules

℞ *Cardizem CD A recommended starting dose is 180-mg capsule daily*

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.

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 REACTION	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%
EGG 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 (i.e., 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.

Product information as of 10/92 (2) BS

MARION MERRELL DOW INC.
PRESCRIPTION PRODUCTS DIVISION
KANSAS CITY, MO 64114

INTRODUCING

THE ONE

CARDIZEM® CD

(diltiazem HCl)

ONCE A DAY

NEW FOR MILD TO MODERATE HYPERTENSIVE PATIENTS

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

20021A2

INTRODUCING

THE ONE

CARDIZEM® CD

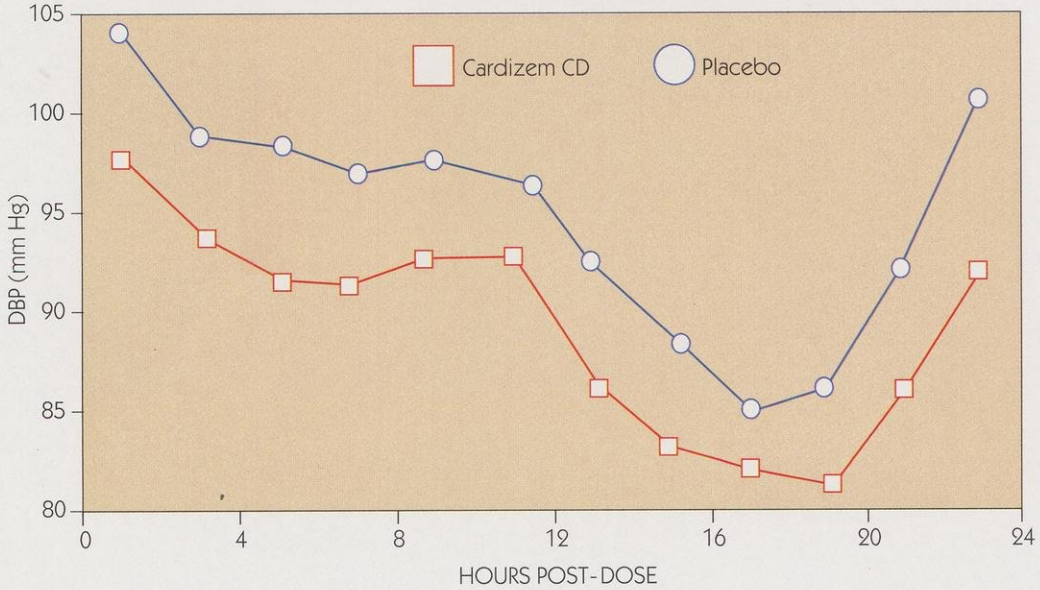
(diltiazem HCl)

ONCE A DAY

PROVIDES PROVEN 24-HOUR BLOOD PRESSURE CONTROL WITH A SINGLE DAILY DOSE

A unique delivery system* designed specifically for diltiazem to provide antihypertensive efficacy

Cardizem CD provides clinically significant blood pressure control over a 24-hour period[1]



Study design: placebo-controlled, crossover trial.

Number of patients: 43 mild to moderate hypertensives.

Treatment period: 12 weeks.

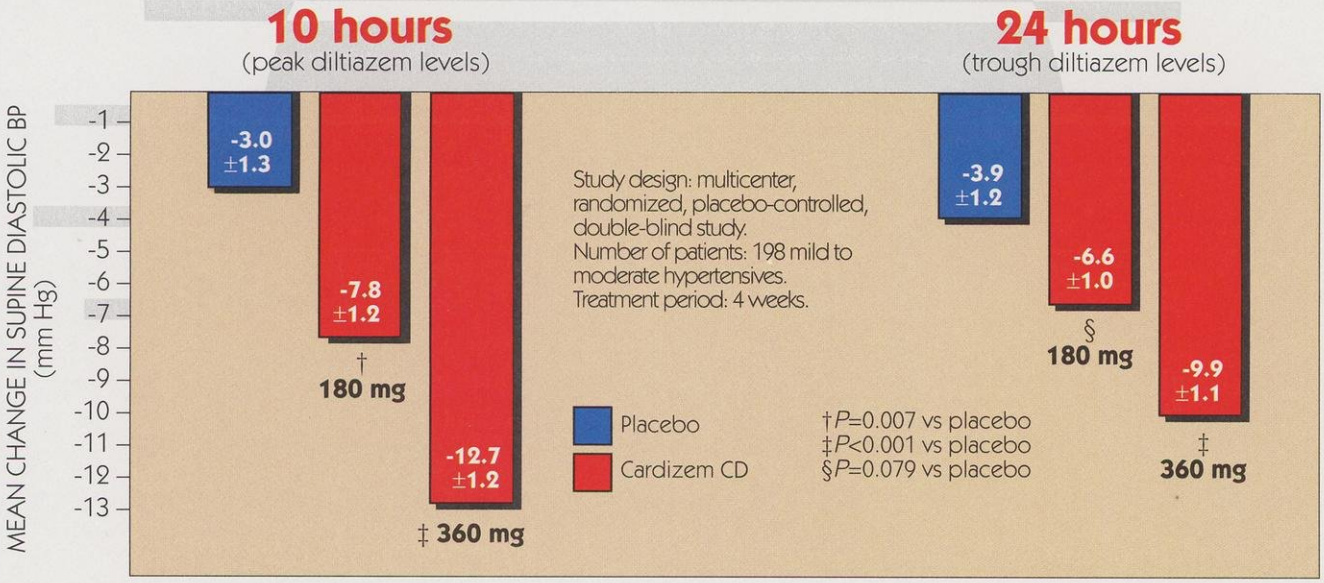
Cardizem CD dosage: 300 mg/day.

* Patent pending.

NEW

PROVEN 24-HOUR EFFICACY

Cardizem CD maintains clinically significant decreases in supine diastolic blood pressure compared to baseline[1]



LOWER PRICE‖

20% lower cost compared to Cardizem® SR (diltiazem HCl) **sustained release capsules**

NEW

ONCE-A-DAY CARDIZEM® CD

(diltiazem HCl)

ONE TO TRUST FOR MILD TO MODERATE HYPERTENSIVE PATIENTS

‖ Based on AWP prices.

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

20021A2

INTRODUCING

THE ONE

CARDIZEM® CD

(diltiazem HCl)

EXCELLENT TOLERABILITY

Rarely associated with vasodilatory or GI side effects[1*]

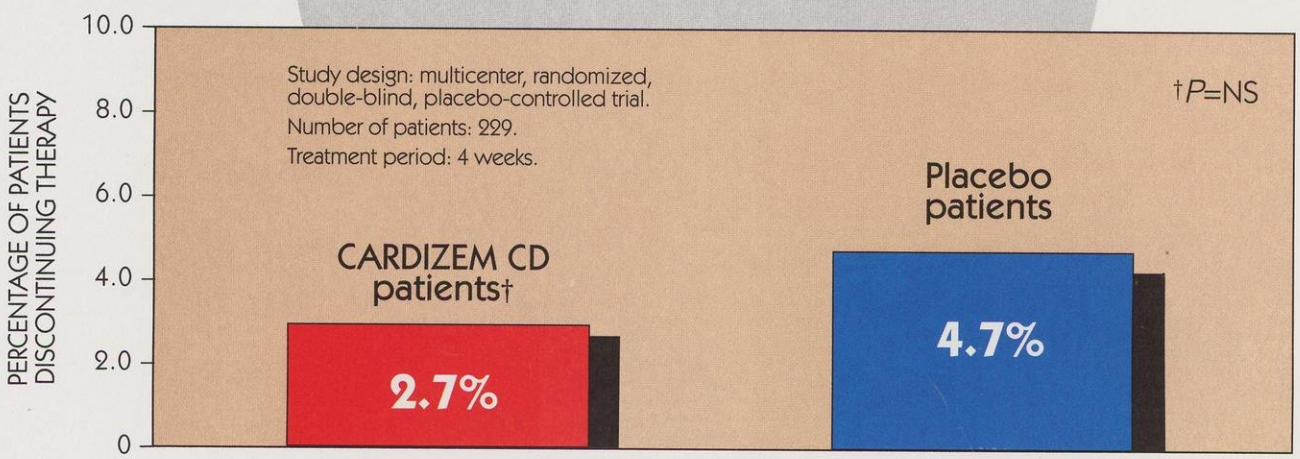
- No reflex tachycardia
- <1% incidence of constipation

Unlike some ACE inhibitors, not associated with cough[1]

* Most commonly reported side effects in placebo-controlled clinical trials include headache, bradycardia, edema, dizziness, ECG abnormality, first-degree AV block, and asthenia.

NEW

A ONCE-A-DAY CALCIUM CHANNEL BLOCKER WITH A DISCONTINUATION RATE COMPARABLE TO PLACEBO



A side-effect profile unlikely to compromise patients with certain concomitant diseases[1-3]

- Including diabetes and coronary artery disease‡

NEW

ONCE-A-DAY CARDIZEM® CD

(diltiazem HCl)

ONE TO TRUST FOR MILD TO MODERATE HYPERTENSIVE PATIENTS

‡ The incidence of hyperglycemia reported with diltiazem has been <1%.

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

20021A2

INTRODUCING

THE ONE

CARDIZEM® CD

(diltiazem HCl)

A FAVORABLE HEMODYNAMIC PROFILE

Decreases peripheral vascular resistance, and does not compromise cardiac output[4]*†

Does not compromise renal blood flow and glomerular filtration rate and decreases renal vascular resistance[4-7]†

Increases coronary blood flow[1,3]

* As seen in patients with normal LV function. Caution should be used in patients with congestive heart failure.

† As seen in studies lasting up to 12 months. The effects of diltiazem on these renal and cardiovascular parameters past 12 months are unknown.

NEW

RARELY CAUSES ADVERSE METABOLIC EFFECTS

No significant changes in total cholesterol and triglycerides[1]

Rarely causes adverse effects on glucose or electrolytes[1,2,8‡]

DOSING INFORMATION

Available as 180-, 240-, and 300-mg dosage strengths

For new patients starting on Cardizem CD:

- Start with one 180-mg capsule daily
- Monitor for 2 weeks; if optimal response is not met
- Titrate to goal blood pressure

For patients switching from Cardizem SR:

- Switch on a total mg/day basis
- If necessary, titrate to goal blood pressure

Once-A-Day

180-mg capsules

240-mg capsules

300-mg capsules

NEW

ONCE-A-DAY CARDIZEM® CD

(diltiazem HCl)

ONE TO TRUST FOR MILD TO MODERATE HYPERTENSIVE PATIENTS

‡ The incidence of hyperglycemia reported with diltiazem has been <1%.

Please see brief summary of prescribing information on next page.

20021A2

NEW

ONCE-A-DAY CARDIZEM® CD

(diltiazem HCl)

ONCE 1 A DAY

ONE TO TRUST

FOR MILD TO MODERATE HYPERTENSIVE PATIENTS

BRIEF SUMMARY

CARDIZEM® CD (diltiazem hydrochloride) Capsules

CARDIZEM® SR (diltiazem hydrochloride) Sustained Release 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 3,007 patients or 0.43%). 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 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 is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters 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 Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any 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. Dosages of similarly metabolized drugs such as cyclosporin, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM 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 concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. 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 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably 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.

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.

Available as Once-A-Day

180-mg capsules

240-mg capsules

300-mg capsules

℞ *Cardizem CD Start with one 180-mg capsule daily*

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 adverse events described below represent events observed in clinical studies of hypertensive patients receiving either CARDIZEM Tablets or CARDIZEM SR Capsules as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients taking CARDIZEM Tablets or CARDIZEM SR Capsules studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and first-degree AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related.

DOUBLE BLIND PLACEBO CONTROLLED HYPERTENSION TRIALS

ADVERSE	DILTIAZEM N=315 # PTS (%)	PLACEBO N=211 # PTS (%)
Headache	38 (12%)	17 (8%)
AV Block First Degree	24 (7.6%)	4 (1.9%)
Dizziness	22 (7%)	6 (2.8%)
Edema	19 (6%)	2 (0.9%)
Bradycardia	19 (6%)	3 (1.4%)
ECG Abnormality	13 (4.1%)	3 (1.4%)
Asthenia	10 (3.2%)	1 (0.5%)
Constipation	5 (1.6%)	2 (0.9%)
Dyspepsia	4 (1.3%)	1 (0.5%)
Nausea	4 (1.3%)	2 (0.9%)
Palpitations	4 (1.3%)	2 (0.9%)
Polyuria	4 (1.3%)	2 (0.9%)
Somnolence	4 (1.3%)	—
Alk Phos Increase	3 (1%)	1 (0.5%)
Hypotension	3 (1%)	1 (0.5%)
Insomnia	3 (1%)	1 (0.5%)
Rash	3 (1%)	1 (0.5%)
AV Block Second Degree	2 (0.6%)	—

The following table presents the most common adverse reactions reported in placebo-controlled trials in patients receiving CARDIZEM CD up to 360 mg with rates in placebo patients shown for comparison.

ADVERSE REACTION	CARDIZEM CD N=324	PLACEBO N=175
HEADACHE	9.0%	8.0%
BRADYCARDIA	4.3%	2.3%
EDEMA	3.7%	2.3%
DIZZINESS	3.1%	3.4%
ECG ABNORMALITY	3.1%	2.9%
AV BLOCK FIRST DEGREE	2.2%	—
ASTHENIA	1.9%	1.7%

In clinical trials of CARDIZEM CD Capsules, CARDIZEM Tablets, and CARDIZEM SR Capsules involving over 3000 patients, the most common events (ie, greater than 1%) were edema (4.9%), headache (4.9%), dizziness (3.5%), asthenia (2.7%), first-degree AV block (2.2%), bradycardia (1.6%), flushing (1.5%), nausea (1.4%), rash (1.3%), and dyspepsia (1.2%).

In addition, the following events were reported infrequently (less than 1%).

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, 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.

HOW SUPPLIED

CARDIZEM® CD (diltiazem hydrochloride) is available as capsules of 180 mg, 240 mg, and 300 mg in bottles of 30 and 90, and in UDIP® packages of 100.

CARDIZEM® SR (diltiazem hydrochloride) is available as sustained release capsules of 60 mg, 90 mg, and 120 mg in bottles of 100, and in UDIP® packages of 100.

Product Information as of October 1991

References: **1.** Data on file, Marion Merrell Dow Inc. **2.** Andrén L, Höglund P, Dotevall A, et al. *Am J Cardiol.* 1988;62:114G-120G. **3.** O'Rourke RA. *Am J Cardiol.* 1985;56:34H-40H. **4.** Amodeo C, Kobrin I, Ventura HO, Messerli FH, Frohlich ED. *Circulation.* 1986;73(1):108-113. **5.** Demarie BK, Bakris GL. *Ann Intern Med.* 1990;113(12):987-988. **6.** Sunderrajan S, Reams G, Bauer JH. *Am Heart J.* 1987;114:383-388. **7.** Isshiki T, Amodeo C, Messerli FH, Pegram BL, Frohlich ED. *Cardiovascular Drugs and Therapy.* 1987;1:359-366. **8.** Frishman WH, Zawacki ET Jr, Smith LK, et al. *Am J Cardiol.* 1987;59:615-623.

MARION MERRELL DOW INC.
PRESCRIPTION PRODUCTS DIVISION
KANSAS CITY, MO 64114

NEW

ONCE-A-DAY CARDIZEM® CD

(diltiazem HCl)

ONE TO SWITCH TO

Easy to switch from Cardizem® SR (diltiazem HCl) **on a total mg/day basis**

Convenient once-a-day dosage for proven 24-hour control[1]

A favorable side-effect profile[1]

Once-a-day dosing schedules result in improved compliance[2]

LOWER PRICE*

20% lower cost than Cardizem® SR capsules

Flexible dosage range

- Start with one 180-mg capsule daily
- Available in 180-, 240-, and 300-mg dosage strengths

*Based on AWP prices.

Cardizem CD is indicated for the treatment of hypertension.

Please see brief summary of prescribing information on next page.

ONCE A DAY

NEW

ONCE-A-DAY CARDIZEM® CD

(diltiazem HCl)

MARION MERRELL DOW INC.
PRESCRIPTION PRODUCTS DIVISION
KANSAS CITY, MO 64114

CCDAE622/A3327

7227T1

ONCE A DAY

NEW

ONCE-A-DAY CARDIZEM® CD

(diltiazem HCl)

Switch from Cardizem® SR on a total mg/day basis

For new patients starting on Cardizem® CD:

- Start with one 180-mg capsule daily
- Monitor for 2 weeks; if optimal response is not met
- Titrate to goal blood pressure

BRIEF SUMMARY

CARDIZEM® CD (diltiazem hydrochloride) Capsules

CARDIZEM® SR (diltiazem hydrochloride) Sustained Release 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 3,007 patients or 0.43%). 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 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 is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters 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 Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any 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. Dosages of similarly metabolized drugs such as cyclosporin, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM 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%. 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 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably 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.

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 adverse events described below represent events observed in clinical studies of hypertensive patients receiving either CARDIZEM Tablets or CARDIZEM SR Capsules as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients taking CARDIZEM Tablets or CARDIZEM SR Capsules studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and first-degree AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related.

DOUBLE BLIND PLACEBO CONTROLLED HYPERTENSION TRIALS

ADVERSE	DILTIAZEM N=315 # PTS (%)	PLACEBO N=211 # PTS (%)
Headache	38 (12%)	17 (8%)
AV Block First Degree	24 (7.6%)	4 (1.9%)
Dizziness	22 (7%)	6 (2.8%)
Edema	19 (6%)	2 (0.9%)
Bradycardia	19 (6%)	3 (1.4%)
ECG Abnormality	13 (4.1%)	3 (1.4%)
Asthenia	10 (3.2%)	1 (0.5%)
Constipation	5 (1.6%)	2 (0.9%)
Dyspepsia	4 (1.3%)	1 (0.5%)
Nausea	4 (1.3%)	2 (0.9%)
Palpitations	4 (1.3%)	2 (0.9%)
Polyuria	4 (1.3%)	2 (0.9%)
Somnolence	4 (1.3%)	—
Alk Phos Increase	3 (1%)	1 (0.5%)
Hypotension	3 (1%)	1 (0.5%)
Insomnia	3 (1%)	1 (0.5%)
Rash	3 (1%)	1 (0.5%)
AV Block Second Degree	2 (0.6%)	—

The following table presents the most common adverse reactions reported in placebo-controlled trials in patients receiving CARDIZEM CD up to 360 mg with rates in placebo patients shown for comparison.

ADVERSE REACTION	CARDIZEM CD N=324	PLACEBO N=175
HEADACHE	9.0%	8.0%
BRADYCARDIA	4.3%	2.3%
EDEMA	3.7%	2.3%
DIZZINESS	3.1%	3.4%
ECG ABNORMALITY	3.1%	2.9%
AV BLOCK FIRST DEGREE	2.2%	—
ASTHENIA	1.9%	1.7%

In clinical trials of CARDIZEM CD Capsules, CARDIZEM Tablets, and CARDIZEM SR Capsules involving over 3000 patients, the most common events (ie, greater than 1%) were edema (4.9%), headache (4.9%), dizziness (3.5%), asthenia (2.7%), first-degree AV block (2.2%), bradycardia (1.6%), flushing (1.5%), nausea (1.4%), rash (1.3%), and dyspepsia (1.2%).

In addition, the following events were reported infrequently (less than 1%).

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, 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.

HOW SUPPLIED

CARDIZEM® CD (diltiazem hydrochloride) is available as capsules of 180 mg, 240 mg, and 300 mg in bottles of 30 and 90, and in UDIP® packages of 100.

CARDIZEM® SR (diltiazem hydrochloride) is available as sustained release capsules of 60 mg, 90 mg, and 120 mg in bottles of 100, and in UDIP® packages of 100.

Product Information as of October 1991

References: **1.** Data on file, Marion Merrell Dow Inc. **2.** Cramer JA, Mattson RH, Prevey ML, et al. *JAMA.* 1989;261(22):3273-3274.

MARION MERRELL DOW INC.
PRESCRIPTION PRODUCTS DIVISION
KANSAS CITY, MO 64114

THE ONE YOU'VE BEEN WAITING FOR

CARDIZEM® CD

(diltiazem HCl)

COMING SOON FROM

MARION MERRELL DOW INC.

PRESCRIPTION PRODUCTS DIVISION

KANSAS CITY, MO 64114

CCDAE501

0341K1

DOWN SAFE

CARDIZEM® SR

(diltiazem HCl) sustained release capsules

For hypertension

Hypertension control, not complaints

CSRAE757

Please see brief summary of prescribing information on next page.

6335K1

Rx Cardizem SR
90 mg
Sig:
Cap i bid

Dosage flexibility:

90 mg SR

120 mg SR

CARDIZEM® SR

(diltiazem HCl) sustained release capsules

For hypertension

- **Unsurpassed efficacy**
- **Low side-effect profile**
- **Convenient bid dosage**

BRIEF SUMMARY
CARDIZEM® SR
(diltiazem hydrochloride)
Sustained Release 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 (nine of 2,111 patients or 0.43%). 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). 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 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 Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any 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. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis 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%. 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 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

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 some reduction in early individual pup weights and survival rates. 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 adverse events described below represent events observed in clinical studies of hypertensive patients receiving either CARDIZEM Tablets or CARDIZEM SR Capsules as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and 1° AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related. The most common events observed in clinical studies (over 2,100 patients) of angina patients and hypertensive patients receiving CARDIZEM Tablets or CARDIZEM SR Capsules were (ie, greater than 1%) edema (5.4%), headache (4.5%), dizziness (3.4%), asthenia (2.8%), first-degree AV block (1.8%), flushing (1.7%), nausea (1.6%), bradycardia (1.5%), and rash (1.5%).

DOUBLE BLIND PLACEBO CONTROLLED HYPERTENSION TRIALS

Adverse	Diltiazem N = 315 # pts (%)	Placebo N = 211 # pts (%)
headache	38 (12%)	17 (8%)
AV block first degree	24 (7.6%)	4 (1.9%)
dizziness	22 (7%)	6 (2.8%)
edema	19 (6%)	2 (0.9%)
bradycardia	19 (6%)	3 (1.4%)
ECG abnormality	13 (4.1%)	3 (1.4%)
asthenia	10 (3.2%)	1 (0.5%)
constipation	5 (1.6%)	2 (0.9%)
dyspepsia	4 (1.3%)	1 (0.5%)
nausea	4 (1.3%)	2 (0.9%)
palpitations	4 (1.3%)	2 (0.9%)
polyuria	4 (1.3%)	2 (0.9%)
somnolence	4 (1.3%)	—
alk phos increase	3 (1%)	1 (0.5%)
hypotension	3 (1%)	1 (0.5%)
insomnia	3 (1%)	1 (0.5%)
rash	3 (1%)	1 (0.5%)
AV block second degree	2 (0.6%)	—

In addition, the following events were reported infrequently (less than 1%) with CARDIZEM SR Capsules or CARDIZEM Tablets or have been observed in angina or hypertension trials.

Cardiovascular: Angina, arrhythmia, second- or third-degree AV block (see conduction warning), bundle branch block, congestive heart failure, syncope, tachycardia, ventricular extrasystoles.

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, nervousness, paresthesia, personality change, tremor.

Gastrointestinal: Anorexia, diarrhea, dry mouth, dysgeusia, mild elevations of SGOT, SGPT, and LDH (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, sexual difficulties, tinnitus.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, erythema multiforme, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. There have been observed cases of a generalized rash, characterized as leukocytoclastic vasculitis. 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 definitive cause and effect relationship between these events and CARDIZEM therapy cannot yet be established. Exfoliative dermatitis (proven by rechallenge) has also been reported.

Issued 1/91

MARION MERRELL DOW INC.
PRESCRIPTION PRODUCTS DIVISION
KANSAS CITY, MO 64114

A NEW ANTIHYPERTENSIVE AGENT THAT PROVIDES THERAPEUTIC BENEFITS

NEW

CARDIZEM® SR

(diltiazem HCl) sustained release capsules

For hypertension

Demonstrated efficacy in a wide range of patients[1]

Low side-effect profile[2]*

Convenient bid dosage

*Most commonly reported side effects in clinical trials include edema, headache, dizziness, asthenia, sinus bradycardia, flushing, and 1° AV block

90 mg SR bid

Please see brief summary of prescribing information on next page.

1592E9

NEW

CARDIZEM® SR

(diltiazem HCl) sustained release capsules

For hypertension

AN AGENT THAT PROVIDES THERAPEUTIC BENEFITS

Starting Dosage:

90 mg bid*

Also Available: 120-mg capsules

*Dosage must be adjusted to each patient's needs, starting with 60 to 120 mg twice daily.

BRIEF SUMMARY
CARDIZEM® SR
(diltiazem hydrochloride)
Sustained Release 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 (nine of 2,111 patients or 0.43%). 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). 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 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 Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any 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. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis 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%. 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 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

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 some reduction in early individual pup weights and survival rates. 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 adverse events described below represent events observed in clinical studies of hypertensive patients receiving either CARDIZEM Tablets or CARDIZEM SR Capsules as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and 1° AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related. The most common events observed in clinical studies (over 2,100 patients) of angina patients and hypertensive patients receiving CARDIZEM Tablets or CARDIZEM SR Capsules were (ie, greater than 1%) edema (5.4%), headache (4.5%), dizziness (3.4%), asthenia (2.8%), first-degree AV block (1.8%), flushing (1.7%), nausea (1.6%), bradycardia (1.5%), and rash (1.5%).

DOUBLE BLIND PLACEBO CONTROLLED HYPERTENSION TRIALS

Adverse	Diltiazem N=315 # pts (%)	Placebo N=211 # pts (%)
headache	38 (12%)	17 (8%)
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ECG abnormality	13 (4.1%)	3 (1.4%)
asthenia	10 (3.2%)	1 (0.5%)
constipation	5 (1.6%)	2 (0.9%)
dyspepsia	4 (1.3%)	1 (0.5%)
nausea	4 (1.3%)	2 (0.9%)
palpitations	4 (1.3%)	2 (0.9%)
polyuria	4 (1.3%)	2 (0.9%)
somnolence	4 (1.3%)	—
alk phos increase	3 (1%)	1 (0.5%)
hypotension	3 (1%)	1 (0.5%)
insomnia	3 (1%)	1 (0.5%)
rash	3 (1%)	1 (0.5%)
AV block second degree	2 (0.6%)	—

In addition, the following events were reported infrequently (less than 1%) or have been observed in angina trials. In many cases, the relation to drug is uncertain.

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Nervous System: Amnesia, depression, gait abnormality, hallucinations, nervousness, paresthesia, personality change, tinnitus, tremor, abnormal dreams.
Gastrointestinal: Anorexia, diarrhea, dysgeusia, mild elevations of SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase, thirst.
Dermatological: Petechiae, pruritus, photosensitivity, urticaria.
Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, sexual difficulties, nasal congestion, nocturia, osteoarticular pain, impotence, dry mouth.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. Definitive cause and effect relationship between these events and CARDIZEM therapy cannot yet be established.

Issued 1/89

References: 1. Pool PE, Seagren SC, Salel AF: *Am J Cardiol* 1985;56:86H-91H. 2. Frishman WH, Zawada ET Jr, Smith LK, et al: *Am J Cardiol* 1987;59:615-623.

Another patient benefit product from

PHARMACEUTICAL DIVISION
MARION LABORATORIES, INC.
KANSAS CITY, MO 64137

CSRAB001
1592E9

HELPING TO ACHIEVE THE FOUR GOALS[1] OF ANTIHYPERTENSIVE THERAPY...

NEW

CARDIZEM® SR

(diltiazem HCl) sustained release capsules

For hypertension

Controls blood pressure[2-6]

Maintains well-being[2-6]

Helps prevent end-organ complications[7,8]

Helps reduce cardiovascular risks[2,5,9]

90 mg SR bid

0930A9

Please see brief summary of prescribing information on next page.

NEW

CARDIZEM® SR

(diltiazem HCl) sustained release capsules

For hypertension

EFFECTIVE MONOTHERAPY WITH HIGH PATIENT ACCEPTANCE

Starting Dosage:

90 mg bid*

Also Available: 120-mg capsules

*Dosage must be adjusted to each patient's needs, starting with 60 to 120 mg twice daily.

BRIEF SUMMARY
CARDIZEM® SR
(diltiazem hydrochloride)
Sustained Release 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 (nine of 2,111 patients or 0.43%). 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.
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3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
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Pediatric Use. Safety and effectiveness in children have not been established.

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polyuria	4 (1.3%)	2 (0.9%)
somnolence	4 (1.3%)	—
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Nervous System: Amnesia, depression, gait abnormality, hallucinations, nervousness, paresthesia, personality change, tinnitus, tremor, abnormal dreams.

Gastrointestinal: Anorexia, diarrhea, dysgeusia, mild elevations of SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase, thirst.

Dermatological: Petechiae, pruritus, photosensitivity, urticaria.

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, sexual difficulties, nasal congestion, nocturia, osteoarticular pain, impotence, dry mouth.

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References: 1. Staessen J, Fagard R, Lignen P, et al: *Pract Cardiol* 1986;12(5):55-65. **2.** Massie B, MacCarthy EP, Ramanathan KB, et al: *Ann Intern Med* 1987;107(2):150-157. **3.** Weir MR, Josselson J, Giard MJ, et al: *Am J Cardiol* 1987;60:361-411. **4.** Frishman WH, Zawada ET Jr, Smith LK, et al: *Am J Cardiol* 1987;59:615-623. **5.** Pool PE, Seagren SC, Salel AF: *Am J Cardiol* 1985;56:86H-91H. **6.** Pool PE, Seagren SC, Salel AF: *Cardiol Board Rev* 1986;3(10):77-91. **7.** Sunderrajan S, Reams G, Bauer JH: *Hypertension* 1986;8:238-242. **8.** Amodeo C, Kobrin I, Ventura HO, et al: *Circulation* 1986;73(1):108-113. **9.** Schulte K-L, Meyer-Sabellek WA, Haertenberger A, et al: *Hypertension* 1986;8:859-865.

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