Original Contributions

Muscle Blood Flow, Insulin Resistance, and Hypertension
Editorial: Vasodilator Action of Hypertension
Effect of Myotrophin on Gene Expression
Hypotensive Response to Increased Renal Perfusion Pressure
Bradykinin Peptides in Blood and Tissues
Cyclosporine and Atrial Natriuretic Peptide
Regional Angiotensin II Production
Nitric Oxide and Lymphoid Dysfunction in SHR
Calcium Fluxes in Hypertension
G Proteins in Genetic Hypertension
Vasodepressor Medullary Neurons and Cardiovascular Control
Coronary Responses to Cerebral Ischemia
Volume Reflex in Borderline Hypertension
Blood Pressure During Sleep in Type I Diabetes
Heart Rate Control in Mild Hypovolemia
Alcohol Moderation Lowers Blood Pressure

Rapid Communication

Vitamin D and Vascular Tone

Personal and Historical Perspectives

Discovery of Angiotensin Peptides and ACE
Now, for hypertension
Once-a-day
DILACOR XR
(diltiazem HCl)
EXTENDED RELEASE CAPSULES

DILACOR XR effectively lowers blood pressure for 24 hours in the majority of patients

DILACOR XR offers the classic diltiazem safety profile across the entire dosing range

DILACOR XR now makes diltiazem a more affordable option for hypertension

BRIEF SUMMARY

CONTRAINDICATIONS
Diltiazem hydrochloride is contraindicated in: (1) patients with sick sinus syndrome or second or third degree AV block in the presence of a functioning pacemaker; (2) patients with second or third degree AV block; (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 as documented by X-ray on admission.

WARNINGS

1. Cardiovascular. Diltiazem hydrochloride 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 abnormal slow heart rates (particularly in patients with sick sinus syndrome) or second or third degree AV block. Diltiazem hydrochloride may result in profound hypotension in some patients. In the absence of carotid sinus reflexes, sudden conversion to second or third degree AV block may result in asystole. 

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 output. In patients with congestive heart failure, there may be increased cardiac filling pressures in the absence of changes in output. Administration of diltiazem hydrochloride concomitantly with propranolol in five normal volunteers resulted in additive effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities (see WARNINGS). As with all drugs, care should be exercised when treating patients with multiple medications.

3. Hypotension. Decreases in blood pressure associated with diltiazem hydrochloride therapy may occasionally result in syncope.

4. Atria Hyperreactivity. Although elevations of serum transaminases and alkaline phosphatase have been observed in clinical studies. Such elevations were usually transient and infrequently reached toxic levels. In most instances, elevations in alanine phosphatase, LDH, SGOT, and other phenomena consistent with acute hepatic injury have not been observed. These reactions tended to occur early after therapy initiation (1 to 6 weeks) and have been reversible upon discontinuance of therapy. The relationship to diltiazem is uncertain in some cases, but probable in some others (see PRECAUTIONS).

PRECAUTIONS

General. Diltiazem hydrochloride is extensively metabolized by the liver and is excreted in the kidney 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 hepatic function or in patients with impaired renal function. In substance and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special human studies, a single dose of 125 mg and higher in rats was associated with the 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 treatment. Cardiomyopathy (see ADVERSE REACTIONS) may be due to diltiazem, although it has not been definitely identified in many cases.

Drug Interactions. Due to the potential for additive effects, caution and careful titration are warranted in patients on digitalis and calcium channel blockers. There have been no reports of interactions in patients with known structure in association with the ingestion of Dilacor XR. In patients receiving diltiazem hydrochloride concomitantly with any agents known to affect cardiac contractility or CNO function (e.g., beta-blockers, digitalis). Patients should be continuously titrated carefully. Due to extensive metabolism, plasma concentra-
American Heart Association
National Research Program

Minority Scientist Development Award

1994-1995

To assist promising scientists who are members of ethnic groups under-represented in the fields of cardiovascular and stroke research (Black, Hispanic, Native American, and Pacific Islander) to develop independent research programs. Junior faculty and clinical faculty seeking basic research training may apply.

Application Deadline
Receipt June 1, 1993
for award activation July, 1994

Information: Division of Research Administration
American Heart Association
7272 Greenville Avenue
Dallas, Texas 75231-4596
(214) 706-1453
(214) 706-1341 (Fax)

Announcement
33rd Annual Conference on Cardiovascular Disease Epidemiology

March 17-20, 1993

Community Studies of CHD Prevention: Progress and Implications

March 20, 1993

Sweeney Convention Center
Santa Fe, New Mexico

Information may be obtained through:
American Heart Association
33rd Annual Conference on Cardiovascular Disease Epidemiology
Scientific and Corporate Meetings
7272 Greenville Avenue
Dallas, TX 75231-4596
(214) 706-1511
Fax: (214) 373-3406

Sponsored by the Council on Epidemiology and Prevention

American Heart Association
NEW ONCE-DAILY NORVASC® (amlodipine besylate)...

In hypertension or angina therapy

CONSIDER THE CARDIOVASCULAR ENVIRONMENT

INTRODUCING ONCE-DAILY

NORVASC®

(amlodipine besylate)

© 1993, Pfizer Inc

Please see brief summary of prescribing information on last page of this advertisement.
Hypertension or angina control that considers the cardiovascular environment.
NEW FOR HYPERTENSION OR ANGINA

NORVASC, a calcium channel blocker (CCB), provides effective yet gentle 24-hour control with intrinsic once-daily dosing

Efficacy

Effective for mild, moderate, and severe hypertension
- Over 80% of patients responding to NORVASC are controlled on 5 mg
- 92% of patients remained on NORVASC for 1 year in a long-term study

Effective for chronic stable and vasospastic angina
- 24-hour angina protection, including the morning hours
- Effective alone or in combination with beta blockers

Safety

Gradual onset of action and minimal adverse effects
- No clinically significant effects on heart rate or cardiac conduction; no negative inotropic effects at clinical doses in hemodynamic studies, even when administered with beta blockers to humans
- Has been used safely in patients with concomitant diseases—Chronic obstructive pulmonary disease, well-compensated Class II-III congestive heart failure (CHF), peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles
- Neutral effect on lipids; no impairment of normal renal function
- No drug interaction with digoxin, warfarin, or cimetidine

Well tolerated: only 1.5% of patients in placebo-controlled trials (n=1730) discontinued NORVASC due to adverse effects
- The most common side effects are headache and edema

SAFETY

- Gradual onset of action and minimal adverse effects
  - No clinically significant effects on heart rate or cardiac conduction; no negative inotropic effects at clinical doses in hemodynamic studies, even when administered with beta blockers to humans
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  - No drug interaction with digoxin, warfarin, or cimetidine

NEW, ONCE-DAILY

NORVASC (amlodipine besylate)

CONFIDENT 24-HOUR CONTROL THAT CONSIDERS THE CARDIOVASCULAR ENVIRONMENT
ONCE-DAILY NORVASC® (amlodipine besylate)...

HYPERTENSION OR ANGINA CONTROL THAT CONSIDERS THE CARDIOVASCULAR ENVIRONMENT

SAFETY

Well tolerated: only 1.5% of patients in placebo-controlled trials (n=1730) discontinued NORVASC due to adverse effects¹

<table>
<thead>
<tr>
<th>Dose-related side effects</th>
<th>NORVASC (%)</th>
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<tr>
<td></td>
<td>5 mg (n=296)</td>
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<tr>
<td>Edema</td>
<td>3.0</td>
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<tr>
<td>Dizziness</td>
<td>3.4</td>
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<tr>
<td>Flushing</td>
<td>1.4</td>
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<tr>
<td>Palpitation</td>
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Caution should be exercised when using CCBs in any patient with heart failure

— In a double-blind study of 118 patients with mild to moderate CHF, NORVASC did not adversely affect cardiac function in patients with impaired LV function (LV ejection fraction < 40%)³

— In this study, NORVASC did not increase plasma norepinephrine levels, and ejection fraction did not change

— Studies in patients with NYHA Class IV heart failure have not been performed

— NORVASC therapy, despite these findings, should be used with caution in patients with heart failure until safety in these patients can be confirmed with additional clinical experience

Please see brief summary of prescribing information on last page of this advertisement.
Intrinsic once-daily dosing

- The usual starting dose is 5 mg in angina or hypertension.

- In hypertension, small, fragile, or elderly individuals or patients with hepatic insufficiency may be started on 2.5 mg once daily.

- Titration can proceed to 10 mg.

- Most angina patients will require 10 mg.

- Can be taken with or without food.

NEW, ONCE-DAILY

NORVASC® (amlodipine besylate) Tablets

For Oral Use

CONTRAINDICATIONS:

NORVASC is contraindicated in patients with known sensitivity to amlodipine.

WARNINGS:

Increased Angina and/or Myocardial Infarction:

Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed increased frequency, duration, or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

PRECAUTIONS:

General:

Since the vasodilation induced by NORVASC is gradual, sudden hypotension has rarely been reported after oral administration of NORVASC. Nonetheless, caution should be exercised when administering NORVASC to patients with severe aortic stenosis.

Use in Patients with Congestive Heart Failure:

Although hemodynamic studies and a controlled trial in NYHA Class III-IV heart failure patients have shown that NORVASC does not lead to clinical depression as measured by exercise tolerance, left ventricular ejection fraction, and clinical symptoms, nor has been studied in patients with NYHA Class III-IV heart failure. In general, all calcium channel blockers should be used with caution in patients with heart failure.

Beta-Blocker Withdrawal:

NORVASC is a beta-blocker and therefore will exert potential cardiovascular risk. Any such withdrawal should be performed gradually over several days; however, it is recommended that the patient be on a therapeutic beta-blocker prior to starting NORVASC.

Drug Interactions:

- In in vitro data in human plasma, NORVASC has shown no effect on the protein binding of drugs (digoxin, phenytoin, warfarin).
- Studies in animals have indicated that the co-administration of NORVASC with digoxin did not change serum digoxin levels or digoxin clearance in normal volunteers; co-administration with phenytoin did not change the phenytoin plasma half-life by more than 25%.
- In clinical trials, NORVASC has been shown to be effective in preventing documented angina attacks in patients with stable angina who were on, or converted from, beta-blockers.
- No drug interactions have been noted when NORVASC was co-administered with digoxin, phenytoin, or warfarin.

DOSING

Intrinsic once-daily dosing

- The usual starting dose is 5 mg in angina or hypertension.

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NOVEL, ONCE-DAILY

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NOVEL, ONCE-DAILY
**CARDIAC OUTPUT COMPUTER**

+CARDIOMAX+ IBM-PC
FOR HUMANS AND RATS

"CARDIOMAX" plus IBM-PC Computer measures, prints on printer and stores on the disc for future recall. *Cardiac Output* Stroke Volume *Heart Rate* Systolic, Diastolic, Mean Blood Pressures *Blood and Injestsate Temperatures *Graphic pictures of Dilution Curve. *Blood Pressure and ECG waveforms *Calculates and prints Dilution Curve's Appearance, Elevation, Mean Concentration and Mean Dilution Times.

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THEY WERE CAREFREE...

They were raised in a simpler time, before sugar-free and fat-free. Now hypertension, often with elevated cholesterol and blood sugar, enters the picture...

NOW THEY'RE CONCERNED...
Today's hypertensives with new concerns...

THE CARDURA

*Adapted from the interim (12 months) results of the Treatment of Mild Hypertension Study, a randomized, double-blind, placebo-controlled trial of a nutritional-hygienic regimen along with various drug therapies. All drugs (except acebutolol) were given initially in low doses. If the patient showed a diastolic blood pressure more than 95 mm Hg on three successive follow-up visits, the dosage was doubled. If blood pressure remained elevated, a second drug (chlorthalidone, except for chlorthalidone group, which was given enalapril) was added. Mean diastolic blood pressure was lowered in the various drug groups with median dosages, as follows: doxazosin (2 mg/day), 12.0 mm Hg; enalapril (5 mg/day), 12.2 mm Hg; chlorthalidone (15 mg/day), 13.1 mm Hg; and acebutolol (400 mg/day), 13.7 mm Hg (n=947, P<0.01 vs placebo).

*n=126, P<0.01 vs placebo. In a pooled analysis of placebo-controlled studies with about 300 predominantly normocholesterolemic patients per treatment group, CARDURA produced a small decrease in total cholesterol (-2.7%) and LDL cholesterol (-4.3%) and a small increase in the HDL/total cholesterol ratio (+4.3%).

*Adapted from Lehtonen et al.* (n=77, after 26 weeks: P<0.001 compared with week 0 for blood pressure and insulin, P<0.05 compared with week 0 for glucose)
Choose CARDURA: first-line therapy for a new generation of hypertensives.

Choose CARDURA for blood pressure control that doesn’t jeopardize blood lipids.

In the Treatment of Mild Hypertension Study, CARDURA lowered diastolic blood pressure (mean 12.0 mm Hg) as effectively as enalapril, chlorthalidone, and acebutolol.

CARDURA lowered blood pressure with a small increase in the HDL/total cholesterol ratio (+2.4%) in the same study. The clinical significance of these changes is uncertain. Cholesterol is just one parameter to consider when selecting the best individualized therapy for a given patient.

Choose CARDURA for blood pressure control that doesn’t compromise blood sugar.

CARDURA controlled diastolic blood pressure without an adverse effect on glucose tolerance or insulin control.

CARDURA is well tolerated. In placebo-controlled studies, only three common side effects were reported significantly more often than placebo: dizziness, somnolence, and fatigue.

Only 2% of patients discontinued therapy due to adverse effects—the same as with placebo.

These were generally mild and transient. Syncope has been reported, but rarely (<1%).

ONCE-A-DAY
CARDURA (doxazosin mesylate) Scored Tablets
1 mg, 2 mg, 4 mg, 8 mg

HYPERTENSION CONTROL FOR A NEW GENERATION.
diuretics or beta-adrenergic blocking agents. There is limited experience
with CARDURA in combination with angiotensin converting enzyme
inhibitors or calcium channel blockers.

**CONTRAINDICATIONS**

CARDURA is contraindicated in patients with a known sensitivity
to quinazolines (e.g. prazosin, terazosin).

**WARNINGS**

Symptomatic and "First-dose" effect.

Doxazosin, like other alpha antagonists, may cause marked hypotension,
syncope and orthostatic hypotension, especially in the supine position, and
other postural syndromes such as dizziness. Marked orthostatic effects
are rare but can also occur when the drug is administered at a
higher dosage, or if therapy is initiated for more than a few days. To
detect such an effect, the patient should be instructed to arise slowly
in the morning, especially if he/she has been lying down or sitting,
and to avoid activities requiring sustained physical effort for several
hours after the first dose of therapy. If hypotension occurs, the patient
should be placed in the supine position.

**ADVERSE REACTIONS**

**Hypotension**

Postural hypotension has been reported, especially with the first dose of
the drug. It is essential that treatment be initiated with the mg dose. The 2, 4,
and 8 mg doses should be titrated slowly (see DOSAGE AND ADMINISTRATION) with increases in dose at weekly intervals.

**Antihypertensive agents should be added with caution.**

Patients being titrated with doxazosin should be cautioned to avoid
activities requiring sustained physical effort for several hours after the
first dose and to avoid driving or operating heavy machinery.

In an early investigational study of the safety and tolerability of increasing
dose of 1 mg, 2 mg, 4 mg, and 8 mg, only 2 of 6 subjects could tolerate more than 2 mg without
experiencing symptoms. The majority of doxazosin male subjects receiving initial doses of 2 mg/day of
doxazosin for up to 12 weeks experienced no significant change in orthostatic hypotension between 0.5 and 6 hours after the first dose necessitating widening of the study. In this study, 8 of the normotensive subjects experienced symptomatic hypotension in hypertensive patients always
dismarked doxazosin at 1 mg/day resulting in a 4% incidence of postural side effects at 1 mg/day with no cases of syncope.

Upon multiple dose clinical trials involving over 1000 patients with
treatment initiated at 1 mg dose and titrated to dose of 1 mg and 1.2 mg,
occurred at 1 mg/day and 0.3% at 2 mg/day and 2 patients treated had
previously treated patients. These patients are sensitive to orthostatic
dysregulation and do not respond to vasopressor therapy. Patients with these
conditions should be treated as evidenced by slower body weight gain and a slightly
closer rate of body weight loss. These patients should be treated as
evidenced by slower body weight gain and a slightly
closer rate of body weight loss. These patients should be treated as
closely as possible to normal weight.

**Orthostatic Hypotension:**

Although orthostatic hypotension is most common with the first dose but can also occur when there is a
rise in plasma renin activity.CARDURA (doxazosin mesylate) is available as colored tablets lor oral
use.

**DOSE AND ADMINISTRATION**

**DOSAGE**

When starting therapy, the usual starting dose of CARDURA is 1 mg/day assuming a patient weight of 60 kg). Myocardial fibrosis was observed
in Wistar rats at maximum doses of 20 mg/kg/day and 100 mg/kg/day. In
rabbits, doxazosin caused an increase in cardiac weights at maximum dose levels of 20 mg/kg/day and 100 mg/kg/day. In
cardiac toxicity in animals:

**Central nervous system:**

- Asthenia
- Impaired concentration;
- Weakness;
- Anorexia;
- Fatigue/malaise;
- and some heart rate disturbance, each about 0.7%.

**Additional adverse reactions have been reported, but these are, in general,
not distinguishable from symptoms that might have occurred in the absence of exposure to doxazosin.**

The following adverse reactions have been reported with a frequency of
between 0.3% and 1%: syncope, headache, insomnia, nervousness, palpitations, paresthesias, rhinitis, rash, stomach pain, sweating.

**Gastrointestinal:**

None known.

**Drug/Laboratory test Interactions:**

Doxazosin is metabolized by the liver and is not excreted in human milk. The concentrations of doxazosin in human milk were not determined. Doxazosin
is a substrate for the human placenta and is partially removed from the maternal circulation after delivery. Doxazosin may interfere with the
placental transport of other substances.

**Pediatric Use:**

Safety and effectiveness in children have not been established.

**Geriatric Use:**

- Patients over 70 years of age had no significant difference in efficacy.

**References:**


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not distinguishable from symptoms that might have occurred in the absence of exposure to doxazosin. The following adverse reactions have been reported with a frequency of between 0.3% and 1%: syncope, headache, insomnia, nervousness, palpitations, paresthesias, rhinitis, rash, stomach pain, sweating.
Molecular Biology of the Normal, Hypertrophied, and Failing Heart

The American Heart Association's Councils on Basic Science, Clinical Cardiology, Circulation, and High Blood Pressure Research will sponsor "Molecular Biology of the Normal, Hypertrophied, and Failing Heart" on August 4-8, 1993, in Asilomar, California. During the sessions physicians and scientists interested in molecular cardiology will hear about state-of-the-art findings from molecular and cell biologists, physiologists, and clinical cardiologists, with the focus on the molecular biology of myocardial hypertrophy and heart failure and the mechanisms involved in decompensation. Topics to be discussed include recent advances that have led to the rapid development of experimental approaches to the study of inherited cardiomyopathies in humans, cardiomyopathic viruses, new techniques of gene transfer, transgenic animals, and cultured myocardial cell models.

The conference will also provide opportunities for formal and informal discussion between molecular biologists working with heart-related systems, scientists using molecular and cellular approaches to the study of myocardial cell structure and function, and clinical cardiologists.

Two poster sessions and two workshops will be held in addition to the nine sessions. During the sessions, which will include question-and-answer periods, speakers will discuss developments in the areas of molecular signaling mechanisms for cardiac hypertrophy; receptor-mediated signaling in the normal and failing heart; cytokine, autocrine, and paracrine factors in cardiac hypertrophy and failure; animal models for left ventricular hypertrophy and failure; excitation-contraction coupling in normal and failing cardiac muscle; molecular, cellular, and biochemical determinants of cardiac contractile dysfunction; molecular genetics and heart muscle dysfunction; and molecular genetics of hypertension.

The preregistration fee is US $200 for AHA council members, $225 for nonmembers, and $90 for residents with a letter of certification from their department head. Preregistration forms must be received at the AHA National Center by July 2, 1993. After that date, fees are $225, $250, and $115, respectively.

Young investigators who hold an academic (or equivalent) rank below associate professor are encouraged to apply for the 30 Young Investigator Awards for conference travel. Travel awards make it possible for young investigators to attend scientific conferences to present research in poster format and to engage in discussion with senior investigators. An abstract, a letter of application, and a curriculum vitae should be sent to the address below. The deadline for receipt of Young Investigator Award applications is February 26, 1993.

Cardiovascular physiologists, pharmacologists, cell biologists, molecular biologists, biochemists, and clinical investigators interested in the pathophysiology of myocardial hypertrophy and heart failure are invited to submit abstracts for the poster sessions. Abstracts must be received by February 26, 1993. For information, call 214-706-1511 or write the American Heart Association, Scientific Conference on Molecular Biology of the Normal, Hypertrophied, and Failing Heart, Scientific and Corporate Meetings, 7272 Greenville Avenue, Dallas, TX 75231-4596.

1993 American Nurses Foundation Grant Program

Approximately 25 awards are given by the American Nurses Foundation each year. Two new awards will also be given in 1993, one from the Allen & Hanburys Respiratory Institute and one jointly funded by Sigma Theta Tau International and the ANF. All applicants must be registered nurses, studies are to be 1 year in length, and separate application must be made to each of the award categories. All awards have an application deadline of May 1, 1993.

Information and application packets are available from ANF, Attn: Nursing Research Grants, 600 Maryland Avenue, SW, Suite 100W, Washington, DC 20024-2571. Telephone 202-554-4444, extension 135.

ADA and NHLBI Sponsor Cardiovascular Risk Factor Management Programs

The American Diabetes Association and the National Heart, Lung, and Blood Institute will sponsor several programs on cardiovascular risk factor management through June 1993. The 3-hour seminars are designed for physicians who treat patients diagnosed with or at risk for atherosclerotic vascular disease, with special emphasis on the patient with diabetes. For more information, contact your local American Diabetes Association affiliate or write Jill Thompson, Professional Programs Specialist, American Diabetes Association,
Grant on Coronary Artery Reactivity Available From the NHLBI

The Division of Heart and Vascular Diseases of the National Heart, Lung, and Blood Institute invites grant applications for up to 5 years of support for research into the roles of sex hormones in the physiology and pathophysiology of the coronary vasculature. The goal is to develop insights into therapeutic approaches for reducing the higher incidence of coronary diseases in men and postmenopausal women than in premenopausal women.

The Public Health Service has initiated a program, "Healthy People 2000," for health promotion and disease prevention. This request for announcements is related to the priority area of heart disease and stroke. Potential applicants may obtain a copy of "Healthy People 2000" (full report, stock number 017-001-00474-0, or summary report, stock number 017-001-00473-1) from the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9325. Telephone 202-783-3238.

Applications may be submitted by domestic and foreign for-profit and nonprofit organizations, public and private. Applications from minorities and women are encouraged.

The research grant application form PHS 398 (revised 9/91), which is to be used in applying for these grants, is available at most institutional offices of sponsored research and may be obtained from the Office of Grants Inquiries, Division of Research Grants, National Institutes of Health, Westwood Building, Room 449, Bethesda, MD 20892. Telephone 301-496-7441.

The deadline for applications is April 27, 1993. Send or deliver a signed, typewritten original of the application and three signed copies to the Division of Research Grants, National Institutes of Health, Westwood Building, Room 240, Bethesda, MD 20892. Send two copies to the Chief, Centers and Special Projects Section, Review Branch, Division of Extramural Affairs, National Heart, Lung, and Blood Institute, Westwood Building, Room 553A, Bethesda, MD 20892. (Applicants who use express mail or a courier service should follow the carrier's requirements for a street address. The address for the Westwood Building is 5333 Westbard Avenue, Bethesda, MD 20816.)

For more information, contact Dr. Isabella Liang, Division of Heart and Vascular Diseases, National Heart, Lung, and Blood Institute, Federal Building, Room 3C06, Bethesda, MD 20892. Telephone 301-496-1081. Fax 301-480-6282.

Grant on Minority Health Available From the NHLBI

The National Heart, Lung, and Blood Institute invites the concurrent submission of small groups of scientifically related research grant applications with a common theme related to minority health issues and issues in the purview of the NHLBI. The goal is to foster collaborative clinical research that focuses on new and improved approaches to diagnosis, management, and prevention of cardiovascular, lung, and blood diseases in minorities. Applicants should have demonstrated expertise in the recruitment and retention of minority study participants.

The special feature of this program is the concurrent submission of research grant applications by investigators who wish to collaborate on a common theme related to clinical research on minority health issues but do not require extensive shared physical resources or core functions to conduct their research. Annual meetings will be sponsored to encourage an exchange of information and ideas among investigators participating in this program. A minimum of three independent investigators with related research objectives should submit concurrent, collaborative, cross-referenced individual research grant applications that address a common theme that spans the traditional boundaries of cardiovascular, lung, and blood research or deals with a single disease or condition from several points of view. Investigators may submit applications for small clinical trials, including biobehavioral and prevention research. Applications will be reviewed for scientific merit, relevance of projects to the chosen theme, and overall proposed collaboration, and special consideration will be given to applications from minority investigators and institutions.

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Applications may be submitted by domestic for-profit and nonprofit organizations, public and private. Awards will not be made to foreign institutions.

Examples of research topics are identification of factors responsible for variability in the clinical presentation, diagnosis, and effectiveness of treatment of cardiovascular diseases; development and evaluation of programs that incorporate strategies for increasing compliance and for long-term maintenance of behavioral changes; refinement of approaches to prevent initiation of smoking and to facilitate smoking cessation; and study of sickle cell disease.

The deadline for applications is March 19, 1993. For more information, contact Patrice Desvignes-Nickens, MD, Division of Heart and Vascular Diseases, National Heart, Lung, and Blood Institute, Federal Building, Room 3C06, Bethesda, MD 20892. Telephone 301-496-1081. Fax 301-480-6282.
Physicians and research investigators are invited to submit abstracts on basic and clinical research in hypertension. Abstracts accepted for presentation will be published in the September issue of *Hypertension*, a journal of the American Heart Association.

Abstract deadline: April 26, 1993

Further information may be obtained through:

American Heart Association
47th Annual Fall Conference and Scientific Sessions
7272 Greenville Avenue
Dallas, TX 75231-4596
(214) 706-1414
Fax: (214) 373-3406

A postdoctoral research training program in U.S. and foreign research centers for individuals who are building cardiovascular or stroke research careers but who are not yet independent.

Application Deadline
Receipt June 1, 1993
for award activation July, 1994

Information: Division of Research Administration
American Heart Association
7272 Greenville Avenue
Dallas, Texas 75231-4596
(214) 706-1453
(214) 706-1341 (Fax)

Participation by women and minority candidates is encouraged.
NEW FOR ANGINA

THE ONE

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

24

ONCE A DAY

© 1992, Merion Merrell Dow Inc.
NEW FOR ANGINA

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

PROVEN 24-HOUR CONTROL

ONCE A DAY

CCDAJ332/A0311

1039T2
IN ANGINA AND HYPERTENSION*

24-hour control through a unique delivery system designed specifically for diltiazem†

CARDIZEM CD provides 24-hour plasma levels similar to those of Cardizem tablets tid at steady state¹

One daily dose provides effective plasma levels¹

* 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.
† Patent pending.
Please see brief summary of prescribing information on adjacent page.
NEW FOR ANGINA

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

PROVEN 24-HOUR EFFICACY

ONCE A DAY
IN ANGINA

Reduces the frequency of angina attacks — through 24 hours

Total angina attacks

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=39)</td>
<td>6.35 ±1.49</td>
<td>4.43 ±1.09</td>
</tr>
<tr>
<td>Cardizem CD 120 mg qd (n=37)</td>
<td>5.36 ±0.73</td>
<td>3.78 ±1.09</td>
</tr>
<tr>
<td>Cardizem CD 360 mg qd (n=40)</td>
<td>4.91 ±0.99</td>
<td>3.40 ±0.53</td>
</tr>
</tbody>
</table>

On Exertion

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=39)</td>
<td>1.33 ±0.41</td>
<td>0.78 ±0.54</td>
</tr>
<tr>
<td>Cardizem CD 120 mg qd (n=37)</td>
<td>2.48 ±0.52</td>
<td>2.73 ±0.71</td>
</tr>
<tr>
<td>Cardizem CD 360 mg qd (n=40)</td>
<td>1.82 ±0.56</td>
<td>0.97 ±0.37</td>
</tr>
</tbody>
</table>

* At rest and on exertion.

IN HYPERTENSION

Consistent antihypertensive effect seen throughout 24 hours

Ambulatory BP subset: 4 of 9 sites performed ambulatory BP monitoring. The 47 patients enrolled at these sites were clinically and demographically representative of the total study population. Mean supine cuff DBP at baseline 99.3 ± 0.6 placebo; 99.4 ± 0.7 Cardizem CD

- Overall study results (127 patients) show a significant mean change at 24 hours in both diastolic (P=0.0075) and systolic (P=0.0009) blood pressure vs placebo
- Cardizem CD average daily dose 268 mg/day

Unlike some once-a-day antihypertensives, titration to bid dosing is not necessary with Cardizem CD

Please see brief summary of prescribing information on adjacent page.
NEW FOR ANGINA

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

EXCELLENT TOLERABILITY WITH CONVENIENT DOSING

ONCE A DAY
IN ANGINA AND HYPERTENSION

Extremely well tolerated

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Cardizem CD n=607</th>
<th>Placebo n=301</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>5.4%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3.0%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>3.3%</td>
<td>1.3%</td>
</tr>
<tr>
<td>AV Block First Degree</td>
<td>3.3%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Edema</td>
<td>2.6%</td>
<td>1.3%</td>
</tr>
<tr>
<td>ECG Abnormality</td>
<td>1.6%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1.8%</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

In clinical trials of Cardizem CD capsules, Cardizem tablets, and Cardizem SR capsules involving over 3200 patients, the most common events (ie, greater than 1%) were edema (4.6%), headache (4.6%), dizziness (3.5%), asthenia (2.6%), first-degree AV block (2.4%), bradycardia (1.7%), flushing (1.4%), nausea (1.4%), and rash (1.2%).

COMPLIANCE-ENHANCING ONCE-DAILY DOSING

For angina or hypertensive patients, a recommended starting dose:
- One 180-mg capsule daily
- If necessary, titrate to optimum response

LOWER PRICE

Based on average wholesale prices using equivalent mg/day doses:
- 35% lower cost than Cardizem® (diltiazem HCl) tablets for angina
  - Cardizem tablets are available as 30, 60, 90, and 120 mg
- 25% lower cost than Cardizem® SR (diltiazem HCl) capsules for hypertension
  - Cardizem SR capsules are available as 60, 90, and 120 mg

Please see brief summary of prescribing information on adjacent page.
CARDIZEM®
(diltiazem HCl)

24-HOUR CONTROL OF ANGINA AND HYPERTENSION

Cardizem CD
Start with one 180-mg capsule daily

Cardizem CD Prescribing Information

Bridal Summary of
Prescribing Information as of October 1992 (2)

CARDIZEM® CD
(diltiazem HCl)

Capsules

CONTRAINDICATIONS
CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with acute myocardial infarction and pulmonary congestion documented by x-ray or adrenalin.

WARNINGS
1. Cardiac Conduction: CARDIZEM prolongs AV node-interval periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may result in decreases in heart rate (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (1/32 of patients or 0.6%). Concomitant use of diltiazem with beta-blockers or digoxin 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 diltiazem.

2. Hypersensitivity: Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have shown a small reduction in cardiac index and consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (fractional shortening 24%) showed improved function in patients with impaired ventricular function without significant decrease in contractile function (dp/dt). Worsening of contractile function has not been reported in patients with pre-existing ventricular dysfunction. 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. Hematologic: Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in synergistic hemodynamic effects.

4. Acute Hepatic Injury: Mild elevations of alanine aminotransferase and aspartate aminotransferase have been noted in clinical studies. Such elevations were usually transient and did not result in discontinuation of treatment. In some instances, significant elevations in enzymes such as alkaline phosphatase, LDH, LDH, and other phenomenon consistent with acute hepatic injury have been noted. These reactions were noted to occur early after therapy initiation (1 to 6 weeks) and have been investigated before discontinuation of drug therapy. The relationship to CARDIZEM therapy in these instances has not been established. (See PRECAUTIONS.)

5. Pregnancy: Nursing Mothers: No information is available on the effects of CARDIZEM on human pregnancy or lactation. Because of the potential for serious adverse reactions in an uncontrolled trial, CARDIZEM should be avoided in nursing mothers.

6. Children: Safety and efficacy of CARDIZEM in children have not been established.

7. Elderly: Geriatric studies of CARDIZEM revealed no evidence of either increased effectiveness or increased toxicity in elderly patients (10% greater than 65 years of age). Cardizem CD capsules involving over 3200 patients, the most common events (ie, greater than 1%) were headache (2.0%), back pain (1.9%), constipation (1.3%), nasopharyngitis, rhinitis and/or pharyngitis (1.3%), dizziness (1.2%), dyspepsia (1.2%), and edema (4.6%). The following table presents the most common adverse reactions reported in placebo-controlled angina and hypertension trials in patients receiving CARDIZEM CD to 350 mg with rates in placebo patients shown for comparison.