Announcement

Scientific Conference on Cardiovascular Response to Exercise

July 24-25, 1992
Fairmont Hotel at Illinois Center
Chicago, Illinois

Information may be obtained through:

American Heart Association
Scientific Conference on Cardiovascular Response to Exercise
Scientific and Corporate Meetings
7272 Greenville Avenue
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American Heart Association
7272 Greenville Avenue
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For rates in Japan, contact:
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For rates in Japan, contact:
Nankodo Co., Ltd.
Cardura (doxazosin mesylate) Tablets

**INDICATIONS AND USAGE**

Cardura is indicated for the treatment of hypertension. Cardura may be used alone or in combination with 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 doxazosin or a pheochromocytoma. **WARNINGS**

Syncpe and “First-dose” Effect: Doxazosin, like other alpha-adrenergic blocking agents, can cause marked hypotension, especially in the upright position, with syncpe and other postural symptoms such as dizziness. Marked orthostatic effects can also occur with the first dose but can also occur when there is a dosage increase, or if therapy is interrupted for more than a few days. As a result, doxazosin should be initiated at dosages of 1 mg and titrated up over the next 2 to 3 weeks to the maximum recommended human dose of about 8 mg/day. There were also reports of syncope and other postural symptoms and fainting on standing in humans. There was no evidence of vasopressor therapy in the Cardura both. In a study of 60 patients receiving doxazosin, 14% of the patients experienced syncpe and other postural symptoms such as dizziness, vertigo, or fainting within 1 hour following the first dose. In this study, 2 of the 60 patients experienced syncpe. Subsequent trials in hypertensive patients always began with an initial dose of 1 mg; however, in 2% of patients, doses ranging from 2 mg to 8 mg were given. If syncpe occurs, the patient should be placed in a recumbent position and treated supportively as necessary. **PRECAUTIONS**

General:

Orthostatic Hypotension: While syncope is the most severe orthostatic effect of Cardura, other symptoms of lowered blood pressure, such as dizziness, light-headedness, or vague, occur, especially during the first 2 to 3 weeks of therapy. These were common in clinical trials, occurring in 2% to 3% of all patients treated and dosed discontinuation of therapy in about 2%. In placebo-controlled clinical trials, hypotensive effects were measured by beginning therapy 1 mg per day and titrating every 7 to 14 days to 2, 4, or 8 mg per day. In this manner, orthostatic hypotension is expected to occur in about 4% of patients treated. These events occurred at the starting dose of 1 mg and 1.2% (2/160) occurred at 16 mg. If syncpe occurs, the patient should be placed in a recumbent position and treated supportively as necessary.

**WARNINGS**

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Treat hypertension at its source with...

ONCE-A-DAY

CARDURA®

(doxazosin mesylate) Scored Tablets
1 mg, 2 mg, 4 mg, 8 mg

CARDURA is well tolerated. Only three common side effects were different from placebo: dizziness, somnolence, and fatigue. These were generally mild and transient; only 2% of patients in placebo-controlled studies discontinued due to adverse effects—the same rate as placebo. Syncope has been reported, but rarely (≤ 1%).

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

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Call for Abstracts

46th Annual Fall Conference and Scientific Sessions of the Council for High Blood Pressure

September 29–October 2, 1992
Stouffer Tower City Plaza Hotel
Cleveland, Ohio

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, 1992

Further information may be obtained through:
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Sponsored by the Council for High Blood Pressure Research
NEW
FROM PARKE-DAVIS

New! ONCE-A-DAY*

ACCUPRIL®
quinaril HCl tablets 10, 20, 40 mg

A Single-handed Approach To Blood Pressure Reduction

* In some patients, the antihypertensive effect may diminish toward the end of the once-daily dosing interval. In such patients, an increase in dosage or twice-daily administration may be warranted.

Please see brief summary of prescribing information on last page of this advertisement.
The ACCUPRIL Single-Agent Commitment™

If, in your medical judgment, your patient requires a diuretic in addition to ACCUPRIL at any time during ACCUPRIL therapy, Parke-Davis will refund your patient’s cost of the diuretic.*

* See DOSAGE AND ADMINISTRATION section of prescribing information.

† Parke-Davis is confident that for many of your hypertensive patients ACCUPRIL will achieve the decrease in blood pressure you expect. However, if, after an adequate trial of ACCUPRIL alone, based on your medical judgment as the prescribing physician, you determine that your patient requires the addition of a diuretic, Parke-Davis will refund to the patient his/her cost for the diuretic prescription less any amount reimbursed or paid for by an HMO, insurance company, or any other plan or program.

For more details, ask your Parke-Davis Representative or call 1-800-955-3077.

† In some patients, the antihypertensive effect may diminish toward the end of the once-daily dosing interval. In such patients, an increase in dosage or twice-daily administration may be warranted.

Please see brief summary of prescribing information on last page of this advertisement.
ACCUPRIL Provides Excellent Inhibition Of Plasma And Tissue ACE

Plasma and Tissue ACE Inhibition

-100 — 0.01 — 0.03 — 0.1 — 1.0

-10 — 20 — 40 — 60 — 80 — 100

Plasma

Tissue

QUINAPRIL (mg/kg)

* In animal studies. Clinical significance correlating tissue ACE inhibition with efficacy has not been established in humans. Adapted from Kaplan et al. Please see brief summary of prescribing information on last page of this advertisement.
Proven ACE Inhibition

- The effect of ACCUPRIL in hypertension appears to result primarily from the inhibition of plasma and tissue ACE activity.
- Correlation of tissue ACE inhibition with efficacy was established in animal studies\(^2\).
- Clinical significance of tissue ACE inhibition has not been established in humans.

* In some patients, the antihypertensive effect may diminish toward the end of the once-daily dosing interval. In such patients, an increase in dosage or twice-daily administration may be warranted. Please see brief summary of prescribing information on last page of this advertisement.
A Single-handed Approach

In Many Patients:
One Agent...
Once-A-Day...
One Price

• Once-a-day dosing*

• One price for all ACCUPRIL tablet strengths... 10 mg, 20 mg, 40 mg

* In some patients, the antihypertensive effect may diminish toward the end of the once-daily dosing interval. In such patients, an increase in dosage or twice-daily administration may be warranted.

ACCUPRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

Please see brief summary of prescribing information on last page of this advertisement.
**Angioedema:** Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE inhibitors, and is fatal if not treated appropriately. Allergic reactions, including anaphylaxis, have been reported with ACE inhibitors. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema. Individuals who have experienced angioedema with an ACE inhibitor cannot be assumed to be non-susceptible to angioedema with other ACE inhibitors. ACE inhibitors should be used cautiously, if at all, in patients with active constrictive pericarditis (see PRECAUTIONS). Where there is evidence of the involvement of the tongue, glottis, or larynx, it is likely to cause airway obstruction. Emergency therapy including, but not limited to, subcutaneous epinephrine (1:1000, 0.3 to 0.5 mL) should be promptly administered.

**Hypotension:** Hypotension, which may be severe and occasionally lead to anuria, has been reported in patients treated with ACE inhibitors. The incidence of hypotension was dose-related in patients with severe renal disease. Elderly patients may be especially susceptible to hypotension. In uncomplicated hypertensive patients treated with ACCUPRIL, symptomatic hypotension was rarely seen, but was more frequently seen in patients with renal impairment, especially if they also have a collagen vascular disease such as systemic lupus erythematosus or scleroderma. ACE inhibitors should be used cautiously, if at all, in patients with renovascular disease (see PRECAUTIONS). Available data from a postmarketing surveillance study in the United States indicate that in patients with active constrictive pericarditis, angioedema occurred in 0.2% of patients treated with ACE inhibitors (see WARNINGS).

**Potassium Levels:** In patients undergoing major surgery or during anesthesia with agents that produce hypotension, ACCUPRIL will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to continued therapy, the starting dose of quinapril should be reduced (see DOSAGE AND ADMINISTRATION).

**Potassium Supplements:** Symptoms of hyperkalemia may be worsened if potassium supplements, or potassium-containing salt substitutes, which should be used cautiously, if at all, in patients treated with agents that produce hypotension (see PRECAUTIONS).

**Serum Creatinine:** Serum creatinine has been observed in some patients following ACE inhibitor therapy. These increases were almost always reversible when discontinuation of the ACE inhibitor and/or diuretic therapy in such patients, renal function should be monitored during therapy. Serum creatinine increases greater than 1.5 times baseline, or an increase of greater than 0.5 mg/dL in patients with chronic renal failure, should prompt the clinician to discontinue the ACE inhibitor and evaluate the patient (see WARNINGS).

**Birth Defects:** In embryonic studies, no adverse effects were seen in some rabbits at quinapril doses as low as 0.5 mg/kg/day (one time the recommended human dose). Quinaprilat was not mutagenic in the Ames bacterial assay when tested at 3.8 to 10 times the maximum human daily dose. Neither Quinapril nor quinaprilat were mutagenic in the mouse micronucleus test. In rabbits, teratogenic effects were observed in some dams and offspring treated with quinapril. Microphthalmia and cleft palate were found in rabbits treated at 10 mg/kg/day (156 times the human dose on a mg/kg basis). In rabbits, maternal toxicity has also been reported, presumably from decreased fetal renin function, oligohydramnios has been associated with limb contractures, craniofacial defects, hypoplastic lung development, and other abnormalities (see PRECAUTIONS).

**Pharmacokinetics:** Quinapril and potassium levels are unchanged during pregnancy. Infants born to mothers who have been treated with ACE inhibitors during the second or third trimester of pregnancy, frequent ultrasound examinations should be performed to look for oligohydramnios. When oligohydramnios is found, the patient should be placed in the left lateral recumbent position and, if necessary, normal saline may be administered in an attempt to replete the renal and fetal circulations (see WARNINGS). If oligohydramnios occurs during the latter half of pregnancy, it may cause a spontaneous premature closure of the fetal ductus arteriosus.

**Healthcare Providers:** Pregnancy Category D. See WARNINGS. Patients receiving diuretics, ACE inhibitors, or angiotensin-converting enzyme inhibitors should be informed that these agents may affect fetal outcome. Prematurity and patent ductus arteriosus have been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure or to the mother's underlying illness. It has not been shown whether exposure limited to the first trimester can cause harmful effects. Drug interaction studies of ACCUPRIL with other agents showed no evidence of increased or decreased toxicities when compared to studies performed with the individual agents in combination (see INTERACTIONS). Patients who have experienced angioedema with an ACE inhibitor cannot be assumed to be non-susceptible to angioedema with other ACE inhibitors. ACCUPRIL has been evaluated for safety in 4960 subjects and patients. Of these, 3203 patients, including 655 elderly patients, were treated in placebo-controlled clinical trials. ACCUPRIL has been evaluated for long-term safety in more than 1400 patients treated for 1 year or more. Adverse experiences were usually mild and transient. Discontinuation of therapy because of adverse events was required in 1 4% of patients treated with ACCUPRIL in placebo-controlled hypertension trials. Adverse experiences probably or possibly related to therapy or to unknown relationship to therapy occurring in 1% or more of the 1583 patients in placebo-controlled hypertension trials who were treated with ACCUPRIL are shown below.

**Geriatric Use:** ACCUPRIL has not been studied specifically in geriatric patients. However, the safety and efficacy of ACCUPRIL in this population have not been established. Adverse experiences have occurred in elderly patients treated with ACE inhibitors that were similar to those seen in younger patients. However, greater sensitivity of some older individual patients cannot be ruled out. The incidence of adverse reactions is only 1.6% higher in patients treated with placebo. The most frequently reported adverse experiences were usually mild and transient. The incidence of adverse reactions was not increased in patients treated with ACCUPRIL compared to placebo. Discontinuation of therapy because of adverse events was required in 0.3% of patients treated with ACCUPRIL in placebo-controlled hypertension trials. Adverse experiences probably or possibly related to therapy or to unknown relationship to therapy occurring in 0.1% or more of the 1583 patients in placebo-controlled hypertension trials who were treated with ACCUPRIL are shown below.

**Drug Interactions:** Drug interaction studies of ACCUPRIL with other agents showed no evidence of increased or decreased toxicities when compared to studies performed with the individual agents in combination (see INTERACTIONS).