FROM SQUIBB RESEARCH

The first and only angiotensin converting enzyme (ACE) inhibitor

CAPOTEN (captopril tablets)
A pharmacologic approach to blood pressure control

Mode of action—A pharmacologic design

Angiotensinogen

\[ \text{Angiotensin I} \]

\[ \text{Renin} \]

\[ \text{Converting Enzyme} \]

\[ \text{Angiotensin II} \]

\[ \text{Vasoconstrictive Activity} \]

\[ \text{Aldosterone Secretion} \]

\[ \text{Increased Total Peripheral Resistance} \]

\[ \text{Sodium \& Water Retention} \]

\[ \text{Increased Blood Pressure} \]

Action of CAPOTEN* (captopril tablets) competitively inhibits angiotensin converting enzyme

Hemodynamic effects—A pharmacologic response

CAPOTEN PRESENTS A FAVORABLE HEMODYNAMIC PROFILE IN HYPERTENSION

<table>
<thead>
<tr>
<th>Study I: Immediate Effects (N=13)</th>
<th>Study II: Longer-Term Effects (N=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (Pretherapy)</td>
<td>Control (Pretherapy)</td>
</tr>
<tr>
<td>CAPOTEN</td>
<td>CAPOTEN</td>
</tr>
</tbody>
</table>

Total Peripheral Resistance

Mean Arterial Blood Pressure

Heart Rate

-60
-50
-40
-30

-150
-140
-130
-120
-110
-100

-90
-80
-70
-60
-50
-40
-30

60
50
40
30

beats/min

units

mm Hg

In two studies of patients with severe essential or renal arterial hypertension, the hemodynamic effects of CAPOTEN* (captopril tablets) were analyzed and compared to pretherapy (control) values in the same subjects. Study I, of 13 patients, showed immediate (at 30 minutes) effects; study II, of 8 patients, showed effects after five to seven days.

Total peripheral resistance was markedly reduced in association with a decrease in mean arterial pressure. There was no significant change in heart rate in early or later studies despite the significant reduction of arterial pressure in both studies.

Additionally, cardiac output immediately and after several days of administration of CAPOTEN was not significantly changed.

Indications and Usage

Because serious adverse reactions (proteinuria; neutropenia/agranulocytosis) have been reported, CAPOTEN is indicated for treatment of hypertensive patients who, on multidrug regimens, either have failed to respond satisfactorily or have developed unacceptable side effects. Usually, multidrug regimens include combinations of a diuretic, a sympathetic nervous system active agent (such as a beta blocker), and a vasodilator.

Please see brief summary on the last page of this advertisement for INDICATIONS, WARNINGS, and ADVERSE REACTIONS.

References:
ACE* INHIBITOR
CAPOTEN®
(captopril tablets)

An unprecedented achievement
in the pharmacotherapeutics of hypertension.

*Angiotensin Converting Enzyme
Distinctive clinical results

**CAPOTEN***(captopril tablets) regimens effective when standard triple therapy (STT) fails in treatment of severe refractory hypertension**

<table>
<thead>
<tr>
<th>Treatment with CAPOTEN</th>
<th>Percent of Cases</th>
<th>Total Favorably Controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Normalized</td>
</tr>
<tr>
<td>All regimens</td>
<td>64</td>
<td>34.4</td>
</tr>
<tr>
<td>STT</td>
<td>29</td>
<td>13.8</td>
</tr>
</tbody>
</table>

In a 14-week comparative study, the effectiveness of therapy with **CAPOTEN** (captopril tablets) was analyzed among severe treatment-refractory hypertensive patients.

During the lead-in period (weeks 1 — 2), patients were treated with standard triple therapy (STT) daily regimen: hydrochlorothiazide, 100 mg; propranolol, 320 mg; and hydralazine, 200 mg. Patients who demonstrated SDBPs greater than 100 mm Hg after the lead-in period were randomized either to continue STT or to receive a regimen involving **CAPOTEN** (alone or, when necessary, with a diuretic or diuretic/beta blocker) for up to 12 weeks.

At eight weeks after randomization, 56% of patients treated with a regimen containing **CAPOTEN** had their blood pressures normalized (SDBP<90 mm Hg) or showed a favorable response (SDBP decreased>10%). This compared with 24% of patients treated with STT Of those patients whose blood pressures normalized on regimens containing **CAPOTEN**, 27% normalized on **CAPOTEN** alone, and 55% normalized on **CAPOTEN** and diuretic—a total of 82%.4

The antihypertensive effects of **CAPOTEN***(captopril tablets) and a diuretic are additive**

<table>
<thead>
<tr>
<th>Week 4</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPOTEN + Diuretic</td>
<td>34.4</td>
</tr>
<tr>
<td>CAPOTEN + Diuretic</td>
<td>21.9</td>
</tr>
</tbody>
</table>

This 12-week study showed the responses of 71 hypertensive patients who after four weeks of **CAPOTEN** alone had not achieved sufficient hypertension control and had a diuretic added. From week 4 to 12, the patients’ mean drop in blood pressure increased from 11% on **CAPOTEN** alone to 24% on **CAPOTEN** with a diuretic. This suggests that the antihypertensive effect of **CAPOTEN** plus a diuretic is additive.4

**Multicenter Studies Confirm Long-Term Effectiveness**

<table>
<thead>
<tr>
<th>Duration of Therapy</th>
<th>Average Systolic Blood Pressure (mm Hg)</th>
<th>Average Diastolic Blood Pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mo (N=591)</td>
<td>150</td>
<td>90</td>
</tr>
<tr>
<td>6 mo (N=540)</td>
<td>150</td>
<td>90</td>
</tr>
<tr>
<td>9 mo (N=373)</td>
<td>150</td>
<td>90</td>
</tr>
<tr>
<td>12 mo (N=210)</td>
<td>150</td>
<td>90</td>
</tr>
</tbody>
</table>

In a long-term multicenter study of **CAPOTEN** (sometimes alone, but usually in combination with other antihypertensive agents), blood pressure measurements at 3, 6, 9, and 12 months indicated continuous hypertension control when compared to the mean pretherapy baseline readings.

The number of patients evaluated at each point varied, because the study was ongoing and patients were continuously entered; 210 were available for follow-up throughout the 12-month period. Only 25 patients (of the total 591) discontinued **CAPOTEN** for therapy-related reasons during the study—7 because of loss of response and 18 because of side effects.4

**References**
4. Data on file. Squibb Institute for Medical Research
An unprecedented achievement in hypertension research.

*Angiotensin Converting Enzyme
Serious adverse reactions reported in clinical trials with CAPOTEN® (captopril tablets)\

- **Proteinuria**
  Proteinuria (levels greater than 1 gm/day) was seen in 1.2% of patients receiving CAPOTEN, and the nephrotic syndrome occurred in about one fourth of these cases. About 60% of affected patients had evidence of prior renal disease. In most cases, proteinuria subsided or cleared within six months, whether or not CAPOTEN was continued, but some patients had persistent proteinuria. Patients receiving CAPOTEN should have urinary protein estimates prior to therapy, at approximately monthly intervals for the first nine months of treatment, and periodically thereafter.

- **Neutropenia/Agranulocytosis**
  Neutropenia (~300/mm³) associated with myeloid hypoplasia was observed in about 0.3% of patients. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. Most of the neutropenic patients had severe hypertension and renal impairment, and about half had systemic lupus erythematosus (SLE), or another autoimmune/collagen disorder.

  CAPOTEN should be used with caution in patients with impaired renal function, serious autoimmune disease (particularly SLE), or who are exposed to other drugs known to affect the white cells or immune response.

  In patients at particular risk (as noted above), white blood cell and differential counts should be performed before starting treatment, at approximately two-week intervals for about the first three months of therapy, and periodically thereafter.

  The risk of neutropenia in patients who are less seriously ill or who receive lower dosages appears to be smaller, and it is sufficient in these patients to have white blood cell counts every two weeks for the first three months of therapy with CAPOTEN, and periodically thereafter. Differential counts should be performed when leukocytes are < 4,000/mm³, or the pretreatment white count is halved.

- **Hypotension**
  Excessive hypotension was rarely seen in hypertensive patients but is a possible consequence of captopril use in severely salt/volume depleted persons such as those treated vigorously with diuretics, for example, patients with severe congestive heart failure (see PRECAUTIONS | Drug Interactions).

Adverse reactions occurring most frequently with CAPOTEN:

- **Skin Rash:** reported in approximately 10% of patients
- **Taste Alteration:** reported in about 7% of patients
- Both effects are generally mild, reversible, or self-limited.

Clinical trials show a particularly low incidence or no reports of the following side effects:

- impotence/loss of libido
- glucose intolerance
- orthostatic effects
- sleep disturbance
- bronchospasm
- bradycardia
- mental depression
- nasal congestion
- cardiac depression
- tachycardia
- fatigue
- hypokalemia

*No reports of this side effect.

Experience in over 4,000 patients

Please see brief summary on the last page of this advertisement. Before prescribing CAPOTEN, INDICATIONS, WARNINGS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections should be carefully reviewed.
An unprecedented achievement in hypertension research.

ACE" INHIBITOR
CAPOTEN®
(captopril tablets)

An unprecedented achievement in hypertension research.

*Angiotensin Converting Enzyme
**CAPOTEN® TABLETS**

**DESCRIPTION**
Capoten (captopril) is a specific competitive inhibitor of angiotensin-I converting enzyme (ACE), the enzyme responsible for converting angiotensin-I to angiotensin-II.

**INDICATIONS**
Because serious adverse effects have been reported (see WARNINGS), Capoten is indicated for treatment of hypertension in patients who on multiple medication has either failed to respond satisfactorily or developed unacceptable side effects. Usually, hydrochlorothiazide and a beta-blocker and, occasionally, a sympathetic nervous system agent (such as a beta-blocker) and a vasodilator

Capoten (captopril) is effective alone, but in the population described above, it should usually be used in combination with other antihypertensive agents who on multiple medication has either failed to respond satisfactorily or developed unacceptable side effects. Usually, hydrochlorothiazide and a beta-blocker and, occasionally, a sympathetic nervous system agent (such as a beta-blocker) and a vasodilator

**WARNING**—Total urinary protein excretion was seen in 1% of patients on captopril, the nephrotic syndrome occurred in about 1 out of 300 patients. Excessive proteinuria (dip-stick on 1st morning urine) or quantitative 24-hr urine—the latter provides greater precision when proteinuria is persistent and/or at low levels) before therapy, at 1- to 2-week intervals, and at the end of therapy. For patients who develop proteinuria > 1/day or increasing proteinuria, the benefits and risks of continuing captopril should be evaluated.

Neutropenia/Anaglobulonemia—Neutropenia (<3000 mm<sup>3</sup>) is associated with myeloid hypoplasia (probably drug related) occurred in about 0.3% of patients. About half of the neutropenic patients developed systemic or oral cavity infections or other features of agranulocytosis. Most of the neutropenic patients who were treated with captopril for at least 1 year had no history of myeloid depression and, in most cases, patients had received 300 mg/d of captopril for 4 or more weeks. The mechanism by which captopril may lead to a significant increase of serum potassium is not known. If the patient has received captopril for less than 2 weeks, is a reasonable risk for developing marked increases in serum potassium. Hypertension, nausea, vomiting, diarrhea, and constipation have occurred in 2% to 5% of patients. If the patient has received captopril for less than 2 weeks, is a reasonable risk for developing a nonanaphylactic shock syndrome. If the patient has received captopril for less than 2 weeks, is a reasonable risk for developing a nonanaphylactic shock syndrome. If the patient has received captopril for less than 2 weeks, is a reasonable risk for developing a nonanaphylactic shock syndrome. If the patient has received captopril for less than 2 weeks, is a reasonable risk for developing a nonanaphylactic shock syndrome. If the patient has received captopril for less than 2 weeks, is a reasonable risk for developing a nonanaphylactic shock syndrome.

**Drug Interactions**

**Adverse Reactions**

**OVERDOSAGE**

**Nursing Mothers**

Concentrations of captopril in human milk are about 1% of those in maternal blood. The effect of low levels of captopril on the nursing infant has not been determined.

Patients on Diuretic Therapy—A precipitous reduction of blood pressure may occur if a diuretic is added to captopril therapy. In patients who are less seriously ill or who receive lower doses of captopril, a modest dose of a thiazide-type diuretic (e.g., hydrochlorothiazide, 25 mg daily) added to captopril therapy may be necessary to reduce captopril dosage and/or discontinuation. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible (see DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]).

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**Pregnancy**

Captopril is secreted in the human milk. Its effect on the nursing infant has not been determined.

**Pediatric**

There is limited experience with use of captopril in children from 2 months to 15 years of age with secondary hypertension and varying degrees of renal insufficiency. Dosage, when needed, has been based on the weight of the child. Captopril should be used in children less than 15 years of age with secondary hypertension and varying degrees of renal insufficiency. For patients who develop proteinuria > 1/day or increasing proteinuria, the benefits and risks of continuing captopril should be evaluated.

**Drug Interactions**

**OVERDOSAGE** Primary concern is correction of hypotension. Volume expansion with an IV infusion of normal saline is the treatment of choice for restoration of blood pressure. PCO<sub>2</sub> may be removed by controlled ventilation or intermittent positive pressure respiration. About 7 of 100 patients developed a diminution or loss of taste perception, taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Weight loss may be associated with the loss of taste. Gastric intolerance, abdominal pain, nausea, vomiting, diarrhea, and constipation may occur, especially in volume-depleted or normovolemic hypertensive patients. In a controlled study of 21 patients with normal renal function and receiving captopril for 4 weeks, adverse reactions to captopril therapy occurred in 29% of patients (see PRECAUTIONS [Drug Interactions]).

Altered Laboratory Findings—Elevated liver enzymes in a low percentage of patients although no correlation with drug therapy or hepatic injury has been established. A single case of hepatitis has been reported in association with captopril use. A transient increase in serum alkaline phosphatase activity may occur, especially in volume-depleted or normovolemic hypertensive patients. In some cases of acute renal failure, severe elevation of serum potassium, the glomerular filtration rate may decrease transiently, also resulting in transient increases in serum creatinine. When dosage reduction is not achieved after 1 or 2 weeks, drug may be added to 50 mg t.i.d. if the blood pressure has not been satisfactorily controlled after another 1 to 2 weeks, and a moderate dose of a thiazide-diohl-uric (e.g., hydrochlorothiazide, 25 mg daily) daily.

The diuretic dose may be increased at 1- to 2-week intervals until its highest usual anti-hypertensive dose is achieved. For patients who develop proteinuria >1 g/day or increasing proteinuria, the benefits and risks of continuing captopril should be evaluated. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible (see DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]).
CARDIAC OUTPUT
BY THERMODILUTION

"CARDIOMAX" model II-R is the only computer which can measure cardiac output of rats (and also guinea pigs, rabbits, dogs, chickens, humans and horses). For rats, it uses unique Columbus Instruments thermodilution microprobes 1/3 mm in size. It also measures systolic, diastolic and mean blood pressures and heart rate up to 1000 beats/minute. Stroke volumes are also automatically computed.

Why Measure Cardiac Output of Rats?
Development of salt sensitive and salt resistant strains of rats provided inexpensive models for studying hypertension. Dynamics of rat circulatory system are similar to dogs or humans. Studies on rats cost only a fraction of studies using dogs.

Automatic Measurements Without Supervision
All parameters (cardiac output, stroke volume, three blood pressures, blood temperature, heart rate, time of day) can automatically be measured periodically and printed when using "CARDIOMAX-II-R" with Columbus Instruments Automatic Injector and Printer.

For more information, write or call

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