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June 15, 2001

Dockets Management Branch (HFA-305)
Docket No. 00N-1263
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857

To Whom It May Concern:

Enclosed you will find the comments from Dr. Joan Davis and Dr. Robert Harmon.

Sincerely,

Dr. Joan Davis

00N-1269

C43

Proposed Label

Overall improved, more readable + organized information.

HIGHLIGHTS OF PRESCRIBING INFORMATION

CAPOTEN® TABLETS
(captopril tablets) ▼Rx

Remove duplicated on next page

WARNING: USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, CAPOTEN should be discontinued as soon as possible. See WARNINGS/PRECAUTIONS: Fetal/Neonatal Morbidity and Mortality (5.5).

RECENT LABELING CHANGES

Indications (1.x)
Warnings/Precautions (5.x, 5.y, 5.z)
Adverse Reactions (8.x)

INDICATIONS AND USAGE

- **Hypertension** (caution in renally-impaired patients), alone or in combination with other anti-hypertensives (1.1)
- **Congestive Heart Failure**, usually in combination with diuretics and digitalis (1.2)
- **Left Ventricular (LV) Dysfunction after Myocardial Infarction** to improve survival and reduce morbidity in clinically stable patients with LV ejection fraction ≤ 40% (1.3)
- **Diabetic Nephropathy** (Type I IDD with proteinuria > 500 mg/day and retinopathy) (1.4)

DOSAGE AND ADMINISTRATION

General: Take 1 hour before meals. Individualize dosage.

Indication	Initiation of Therapy	Usual Daily Dose	Do Not Exceed
Hypertension	25 mg bid or tid	25-150 mg bid or tid*	450 mg/day
Heart Failure	25 mg tid	50-100 mg tid	450 mg/day
LV Dysfunction after MI	12.5 mg tid†	50 mg tid	
Diabetic Nephropathy		25 mg tid	

* Usual daily dosing does not exceed 50 mg BID or TID. Consider adding a thiazide-type diuretic. (2.2)
† A single dose of 6.25 mg should precede initiation of 12.5 mg therapy. (2.4)
Adjust dose in renal impairment (2.6, 5.7)

This should be highlighted and enlarged

HOW SUPPLIED

Tablets: 12.5, 25, 50, 100 mg; scored (3)

CONTRAINDICATIONS

Known hypersensitivity (e.g., angioedema) to any ACE inhibitor.

WARNINGS/PRECAUTIONS

- Angioedema with possibility of airway obstruction (5.1)
- Neutropenia (<1000/mm³) with myeloid hypoplasia (5.2)
- Excessive hypotension (5.4)
- Fetal/Neonatal Morbidity and Mortality (5.5)
- Hepatic failure (5.6)
- Use with caution in renal impairment. (2.6, 5.7)
- Hyperkalemia (5.8)
- Cough (5.9)

Most Common Adverse Reactions (≥ n/100) (8)

- rash (sometimes with arthralgia and eosinophilia), taste impairment (diminution or loss), cough, pruritus, chest pain, palpitations, tachycardia, proteinuria

To report SUSPECTED SERIOUS ADRs, call (manufacturer) at (phone #) or FDA's MedWatch at 1-800-FDA-1088

This is an improvement and may ↑ the reporting of ADR's to the FDA

DRUG INTERACTIONS

- Diuretics (6.1)
- Other vasodilators (6.2)
- Agents Causing Renin Release (6.3)
- Beta-Blockers (6.4)
- Agents Increasing Serum Potassium (6.5)
- Lithium (6.7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Fetal/Neonatal Morbidity and Mortality (5.5)
- Lactating Women: Potential for serious adverse reactions in nursing infants. (7.3)
- Pediatric Use: Safety and effectiveness not established. Use only if other measures ineffective. (7.4)
- Renal-impairment: Use with caution. (2.6, 5.7)

See P for PATIENT COUNSELING INFORMATION

These highlights do not include all the information needed to prescribe Capoten safely and effectively. See Capoten's comprehensive prescribing information provided below.

m/yy

COMPREHENSIVE PRESCRIBING INFORMATION: INDEX – This is good as a road map

COMPREHENSIVE PRESCRIBING INFORMATION

Put under warnings/precautions

! WARNING: USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, CAPOTEN should be discontinued as soon as possible. See WARNINGS/PRECAUTIONS: Fetal/Neonatal Morbidity and Mortality (5.5).

1 INDICATIONS AND USAGE

1.1 **Hypertension:** CAPOTEN is indicated for the treatment of hypertension.

In using CAPOTEN, consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS/PRECAUTIONS).

CAPOTEN (captopril) may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for hypertensives who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations.

CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics. The blood pressure lowering effects of captopril and thiazides are approximately additive.

1.2 **Heart Failure:** CAPOTEN is indicated in the treatment of congestive heart failure usually in combination with diuretics and digitalis. The beneficial effect of captopril in heart failure does not require the presence of digitalis, however, most controlled clinical trial experience with captopril has been in patients receiving digitalis, as well as diuretic treatment.

1.3 **Left Ventricular Dysfunction After Myocardial Infarction:** CAPOTEN is indicated to improve survival following myocardial infarction in clinically stable patients with left ventricular dysfunction manifested as an ejection fraction ≤ 40% and to reduce the incidence of overt heart failure and subsequent hospitalizations for congestive heart failure in these patients.

1.4 **Diabetic Nephropathy:** CAPOTEN is indicated for the treatment of diabetic nephropathy (proteinuria >500 mg/day) in patients with type I insulin-dependent diabetes mellitus and retinopathy. CAPOTEN decreases the rate of progression of renal insufficiency and development of serious adverse clinical outcomes (death or need for renal transplantation or dialysis).

(*) Include statement about ACE in blacks

2 DOSAGE AND ADMINISTRATION

2.1 CAPOTEN (captopril) should be taken one hour before meals. Dosage must be individualized.

2.2 **Hypertension:** Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure elevation, salt restriction, and other clinical circumstances. If possible, discontinue the patient's previous antihypertensive drug regimen for one week before starting CAPOTEN.

The initial dose of CAPOTEN is 25 mg bid or tid. If satisfactory reduction of blood pressure has not been achieved after one or two weeks, the dose may be increased to 50 mg bid or tid. Concomitant sodium restriction may be beneficial when CAPOTEN (captopril) is used alone.

The dose of CAPOTEN in hypertension usually does not exceed 50 mg tid. Therefore, if the blood pressure has not been satisfactorily controlled after one to two weeks at this dose, (and the patient is not already receiving a diuretic), a modest dose of a thiazide-type diuretic (e.g., hydrochlorothiazide, 25 mg daily), should be added. The diuretic dose may be increased at one- to two-week intervals until its highest usual antihypertensive dose is reached.

If CAPOTEN is being started in a patient already receiving a diuretic, CAPOTEN therapy should be initiated under close medical supervision (see DRUG INTERACTIONS regarding hypotension (6.1)), with dosage and titration of CAPOTEN as noted above.

If further blood pressure reduction is required, the dose of CAPOTEN may be increased to 100 mg bid or tid and then, if necessary, to 150 mg bid or tid (while continuing the diuretic).

The usual dose range is 25 to 150 mg bid or tid. A maximum daily dose of 450 mg CAPOTEN should not be exceeded.

For patients with severe hypertension (e.g., accelerated or malignant hypertension), when temporary discontinuation of current antihypertensive therapy is not practical or desirable, or when prompt titration to more normotensive blood pressure levels is indicated, diuretic should be continued but other current antihypertensive medication stopped and CAPOTEN dosage promptly initiated at 25 mg bid or tid, under close medical supervision.

When necessitated by the patient's clinical condition, the daily dose of CAPOTEN may be increased every 24 hours or less under continuous medical supervision until a satisfactory blood pressure response is obtained or the maximum dose of CAPOTEN is reached. In this regimen, addition of a more potent diuretic, e.g., furosemide, may also be indicated.

Beta-blockers may also be used in conjunction with CAPOTEN therapy (see DRUG INTERACTIONS (6.4)), but the effects of the two drugs are less than additive.

2.3 **Heart Failure:** Initiation of therapy requires consideration of recent diuretic therapy and the possibility of severe salt/volume depletion. In patients with either normal or low blood pressure, who have been vigorously treated with diuretics and who may be hyponatremic and/or hypovolemic, a starting dose of 6.25 or 12.5 mg tid may minimize the magnitude or duration of the hypotensive effect (see WARNINGS/PRECAUTIONS: Hypotension (5.4)); for these patients, titration to the usual daily dosage can then occur within the next several days.

For most patients the usual initial daily dosage is 25 mg tid. After a dose of 50 mg tid is reached, further increases in dosage should be delayed, where possible, for at least two weeks to determine if a satisfactory response occurs. Most patients studied have had a satisfactory clinical improvement at 50 or 100 mg tid. A maximum daily dose of 450 mg of CAPOTEN should not be exceeded.

CAPOTEN should generally be used in conjunction with a diuretic and digitalis. CAPOTEN therapy must be initiated under very close medical supervision.

2.4 **Left Ventricular Dysfunction After Myocardial Infarction:** The recommended dose for long-term use in patients following a myocardial infarction is a target maintenance dose of 50 mg tid.

Therapy may be initiated as early as three days following a myocardial infarction. After a single dose of 6.25 mg, CAPOTEN therapy should be initiated at 12.5 mg tid. CAPOTEN should then be increased to 25 mg tid during the next several days and to a target dose of 50 mg tid over the next several weeks as tolerated (see CLINICAL PHARMACOLOGY (12.2)).

CAPOTEN may be used in patients treated with other post-myocardial infarction therapies, e.g., thrombolytics, aspirin, beta blockers.

2.5 **Diabetic Nephropathy:** The recommended dose of CAPOTEN for long term use to treat diabetic nephropathy is 25 mg tid.

Other antihypertensives such as diuretics, beta blockers, centrally acting agents or vasodilators may be used in conjunction with CAPOTEN if additional therapy is required to further lower blood pressure.

2.6 **Dosage Adjustment in Renal Impairment:** Because CAPOTEN is excreted primarily by the kidneys, excretion rates are reduced in patients with impaired renal function. These patients will take longer to reach steady-state captopril levels and will reach higher steady-state levels for a given daily dose than patients with normal renal function. Therefore, these patients may respond to smaller or less frequent doses.

Accordingly, for patients with significant renal impairment, initial daily dosage of CAPOTEN should be reduced, and smaller increments utilized for titration, which should be quite slow (one- to two-week intervals). After the desired therapeutic effect has been achieved, the dose should be slowly back-titrated to determine the minimal effective dose. When concomitant diuretic therapy is required, a loop diuretic (e.g., furosemide), rather than a thiazide diuretic, is preferred in patients with severe renal impairment. (See also WARNINGS/PRECAUTIONS: Hemodialysis (5.12))

3 HOW SUPPLIED

12.5 mg tablets in bottles of 100 and 1000, 25 mg tablets in bottles of 100 and 1000, 50 mg tablets in bottles of 100 and 1000, and 100 mg tablets in bottles of 100. Bottles contain a desiccant-charcoal canister.

Unimatic unit-dose packs containing 100 tablets are also available for each potency: 12.5 mg, 25 mg, 50 mg, and 100 mg.

The 12.5 mg tablet is a biconvex oval with a partial bisect bar; the 25 mg tablet is a biconvex rounded square with a quadrisect bar; the 50 and 100 mg tablets are biconvex ovals with a bisect bar. All captopril tablets are white and may exhibit a slight sulfurous odor.

Storage: Do not store above 86° F. Keep bottles tightly closed (protect from moisture).

4 CONTRAINDICATIONS

CAPOTEN (captopril) is contraindicated in patients who are hypersensitive to this product or any other angiotensin-converting enzyme inhibitor (e.g., a patient who has experienced angioedema during therapy with any other ACE inhibitor).

5 WARNINGS/PRECAUTIONS

good to repeat this info as currently reporting of ADRs is low.

To report SUSPECTED SERIOUS ADRs, call (manufacturer) at (phone #) or FDA's MedWatch at 1-800-FDA-1088

5.1 Angioedema

Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been seen in patients treated with ACE inhibitors, including captopril. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Emergency therapy, including but not necessarily limited to, subcutaneous administration of a 1:1000 solution of epinephrine should be promptly instituted.

Swelling confined to the face, mucous membranes of the mouth, lips and extremities has usually resolved with discontinuation of captopril; some cases required medical therapy. (See PATIENT COUNSELING INFORMATION (P) and ADVERSE REACTIONS (8).)

5.2 Neutropenia/Agranulocytosis

Neutropenia (<1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis.

The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed.

In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk of neutropenia in clinical trials was about 1 per 500, a frequency over 15 times that for uncomplicated hypertension. Daily doses of captopril were relatively high in these patients, particularly in view of their diminished renal function. In foreign marketing experience in patients with renal failure, use of allopurinol concomitantly with captopril has been associated with neutropenia but this association has not appeared in U.S. reports.

In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7 percent of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. About half of the reported cases had serum creatinine ≥ 1.6 mg/dL and more than 75 percent were in patients also receiving procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

The neutropenia has usually been detected within three months after captopril was started. Bone marrow examinations in patients with neutropenia consistently showed myeloid hypoplasia, frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen.

In general, neutrophils returned to normal in about two weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13 percent of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors.

Evaluation of the hypertensive or heart failure patient should always include assessment of renal function. If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately two-week intervals for about three months, then periodically.

In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution.

All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, white cell counts should be performed without delay.

Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) the physician should withdraw captopril and closely follow the patient's course.

5.3 Proteinuria

Total urinary proteins greater than 1 g per day were seen in about 0.7 percent of patients receiving captopril. About 90 percent of affected patients had evidence of prior renal disease or received relatively high doses of captopril (in excess of 150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within six months whether or not captopril was continued. Parameters of renal function, such as BUN and creatinine, were seldom altered in the patients with proteinuria.

5.4 Hypotension

Excessive hypotension was rarely seen in hypertensive patients but is a possible consequence of captopril use in salt/volume depleted persons (such as those treated vigorously with diuretics), patients with heart failure or those patients undergoing renal dialysis. (See DRUG INTERACTIONS (6.1).)

In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure greater than 20 percent were recorded in about half of the patients. This transient hypotension is more likely to occur after any of the first several doses and is usually well tolerated, producing either no symptoms or brief mild lightheadedness, although in rare instances it has been associated with arrhythmia or conduction defects. Hypotension was the reason for discontinuation of drug in 3.6 percent of patients with heart failure.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first two weeks of treatment and whenever the dose of captopril and/or diuretic is increased. In patients with heart failure, reducing the dose of diuretic, if feasible, may minimize the fall in blood pressure.

Hypotension is not *per se* a reason to discontinue captopril. Some decrease of systemic blood pressure is a common and desirable observation upon initiation of CAPOTEN (captopril) treatment in heart failure. The magnitude of the decrease is greatest early in the course of treatment; this effect stabilizes within a week or two, and generally returns to pretreatment levels, without a decrease in therapeutic efficacy, within two months.

5.5 Fetal/Neonatal Morbidity and Mortality

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury,

including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of captopril as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, captopril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. While captopril may be removed from the adult circulation by hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril; there is no information concerning exchange transfusion for removing captopril from the general circulation.

When captopril was given to rabbits at doses about 0.8 to 70 times (on a mg/kg basis) the maximum recommended human dose, low incidences of craniofacial malformations were seen. No teratogenic effects of captopril were seen in studies of pregnant rats and hamsters. On a mg/kg basis, the doses used were up to 150 times (in hamsters) and 625 times (in rats) the maximum recommended human dose.

5.6 Hepatic Failure

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

5.7 Impaired Renal Function

Hypertension--Some patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine after reduction of blood pressure with captopril. Captopril dosage reduction and/or discontinuation of diuretic may be required. For some of these patients, it may not be possible to normalize blood pressure and maintain adequate renal perfusion.

Heart Failure--About 20 percent of patients develop stable elevations of BUN and serum creatinine greater than 20 percent above normal or baseline upon long-term treatment with captopril. Less than 5 percent of patients, generally those with severe preexisting renal disease, required discontinuation of treatment due to progressively increasing creatinine; subsequent improvement probably depends upon the severity of the underlying renal disease.

See CLINICAL PHARMACOLOGY (12), DOSAGE AND ADMINISTRATION (2.6), ADVERSE REACTIONS: Altered Laboratory Findings (8.1).

5.8 Hyperkalemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including captopril. When treated with ACE inhibitors, patients at risk for the development of hyperkalemia include those with: renal insufficiency; diabetes mellitus; and those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or other drugs associated with increases in serum potassium. In a trial of type I diabetic patients with proteinuria, the incidence of withdrawal of treatment with captopril for hyperkalemia was 2% (4/207). In two trials of normotensive type I diabetic patients with microalbuminuria, no captopril group subjects had hyperkalemia (0/116). (See PATIENT COUNSELING INFORMATION (P); DRUG INTERACTIONS (6.5); ADVERSE REACTIONS: Altered Laboratory Findings (8.1).)

5.9 Cough

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

5.10 Valvular Stenosis

There is concern, on theoretical grounds, that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators because they do not develop as much afterload reduction as others.

5.11 Surgery/Anesthesia

In patients undergoing major surgery or during anesthesia with agents that produce hypotension, captopril will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

5.12 Hemodialysis

Recent clinical observations have shown an association of hypersensitivity-like (anaphylactoid) reactions during hemodialysis with high-flux dialysis membranes (e.g., AN69) in patients receiving ACE inhibitors. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of medication.

6 DRUG INTERACTIONS

6.1 Hypotension--Patients on Diuretic Therapy

Patients on diuretics and especially those in whom diuretic therapy was recently instituted, as well as those on severe dietary salt restriction or dialysis, may occasionally experience a precipitous reduction of blood pressure usually within the first hour after receiving the initial dose of captopril.

The possibility of hypotensive effects with captopril can be minimized by either discontinuing the diuretic or increasing the salt intake approximately one week prior to initiation of treatment with CAPOTEN or initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least one hour after the initial dose. If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of normal saline. This transient hypotensive response is not a contraindication to further doses which can be given without difficulty once the blood pressure has increased after volume expansion.

6.2 Agents Having Vasodilator Activity

Data on the effect of concomitant use of other vasodilators in patients receiving CAPOTEN for heart failure are not available; therefore, nitroglycerin or other nitrates (as used for management of angina) or other drugs having vasodilator activity should, if possible, be discontinued before starting CAPOTEN. If resumed during CAPOTEN therapy, such agents should be administered cautiously, and perhaps at lower dosage.

6.3 Agents Causing Renin Release

Captopril's effect will be augmented by antihypertensive agents that cause renin release. For example, diuretics (e.g., thiazides) may activate the renin-angiotensin-aldosterone system.

6.4 Agents Affecting Sympathetic Activity

The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Therefore, agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking

agents) should be used with caution. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive.

6.5 Agents Increasing Serum Potassium

Since captopril decreases aldosterone production, elevation of serum potassium may occur. Potassium-sparing diuretics such as spironolactone, triamterene, or amiloride, or potassium supplements should be given only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Salt substitutes containing potassium should also be used with caution.

6.6 Inhibitors Of Endogenous Prostaglandin Synthesis

It has been reported that indomethacin may reduce the antihypertensive effect of captopril, especially in cases of low renin hypertension. Other nonsteroidal anti-inflammatory agents (e.g., aspirin) may also have this effect.

6.7 Lithium

Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be coadministered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

6.8 Drug/Laboratory Test Interaction

Captopril may cause a false-positive urine test for acetone.

7 USE IN SPECIFIC POPULATIONS

7.1 Pregnancy Categories C (first trimester) and D (second and third trimesters) See WARNINGS/PRECAUTIONS: Fetal/Neonatal Morbidity and Mortality (5.5).

7.3 Lactating Women

Concentrations of captopril in human milk are approximately one percent of those in maternal blood. Because of the potential for serious adverse reactions in nursing infants from captopril, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of CAPOTEN (captopril) to the mother. (See USE IN SPECIFIC POPULATIONS: Pediatric Use (7.4).)

7.4 Pediatric Use

Safety and effectiveness in children have not been established. There is limited experience reported in the literature with the use of captopril in the pediatric population; dosage, on a weight basis, was generally reported to be comparable to or less than that used in adults.

Infants, especially newborns, may be more susceptible to the adverse hemodynamic effects of captopril. Excessive, prolonged and unpredictable decreases in blood pressure and associated complications, including oliguria and seizures, have been reported.

CAPOTEN (captopril) should be used in children only if other measures for controlling blood pressure have not been effective.

7.5 Include statement about ACE in blacks (precautions)

8 ADVERSE REACTIONS

Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal: About one of 100 patients developed proteinuria (see WARNINGS/PRECAUTIONS (5.3)).

Each of the following has been reported in approximately 1 to 2 of 1000 patients and are of uncertain relationship to drug use: renal insufficiency, renal failure, nephrotic syndrome, polyuria, oliguria, and urinary frequency.

Hematologic: Neutropenia/agranulocytosis has occurred (see WARNINGS/PRECAUTIONS (5.2)). Cases of anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic: Rash, often with pruritus, and sometimes with fever, arthralgia, and eosinophilia, occurred in about 4 to 7 (depending on renal status and dose) of 100 patients, usually during the first four weeks of therapy. It is usually maculopapular, and rarely urticarial. The rash is usually mild and disappears within a few days of dosage reduction, short-term treatment with an antihistaminic agent, and/or discontinuing therapy; remission may occur even if captopril is continued. Pruritus, without rash, occurs in about 2 of 100 patients. Between 7 and 10 percent of patients with skin rash have shown an eosinophilia and/or positive ANA titers. A reversible associated pemphigoid-like lesion, and photo sensitivity, have also been reported.

Flushing or pallor has been reported in 2 to 5 of 1000 patients.

Cardiovascular: Hypotension may occur; see DRUG INTERACTIONS (6.1) for discussion of hypotension with captopril therapy.

Tachycardia, chest pain, and palpitations have each been observed in approximately 1 of 100 patients.

Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure have each occurred in 2 to 3 of 1000 patients.

Dysgeusia: Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception. Taste impairment is reversible and usually self-limited (2 to 3 months) even with continued drug administration. Weight loss may be associated with the loss of taste.

Angioedema: Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been reported in approximately one in 1000 patients. Angioedema involving the upper airways has caused fatal airway obstruction. (See PATIENT COUNSELING INFORMATION (P).)

Cough: Cough has been reported in 0.5-2% of patients treated with captopril in clinical trials. (See WARNINGS/PRECAUTIONS: Cough (5.9).)

The following have been reported in about 0.5 to 2 percent of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials: gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, alopecia, paresthesias.

Other clinical adverse effects reported since the drug was marketed are listed below by body system. In this setting, an incidence or causal relationship cannot be accurately determined.

Body as a whole: Anaphylactoid reactions (see WARNINGS/PRECAUTIONS: Hemodialysis (5.12)).

General: Asthenia, gynecomastia.

Cardiovascular: Cardiac arrest, cerebrovascular accident/insufficiency, rhythm disturbances, orthostatic hypotension, syncope.

Dermatologic: Bullous pemphigus, erythema multiforme (including Stevens-Johnson syndrome), exfoliative dermatitis.

Gastrointestinal: Pancreatitis, glossitis, dyspepsia.

Hematologic: Anemia, including aplastic and hemolytic.

Hepatobiliary: Jaundice, hepatitis, including rare cases of necrosis, cholestasis.

Metabolic: Symptomatic hyponatremia.

Musculoskeletal: Myalgia, myasthenia.

Nervous/Psychiatric: Ataxia, confusion, depression, nervousness, somnolence.

Respiratory: Bronchospasm, eosinophilic pneumonitis, rhinitis.

Special Senses: Blurred vision.

Urogenital: Impotence.

As with other ACE inhibitors, a syndrome has been reported which may include: fever, myalgia, arthralgia, interstitial nephritis, vasculitis, rash or other dermatologic manifestations, eosinophilia and an elevated ESR.

Fetal/Neonatal Morbidity and Mortality

See WARNINGS/PRECAUTIONS: Fetal/Neonatal Morbidity and Mortality.

8.1 Altered Laboratory Findings

Serum Electrolytes: Hyperkalemia: small increases in serum potassium, especially in patients with renal impairment (see WARNINGS/PRECAUTIONS (5.8)).

Hyponatremia: particularly in patients receiving a low sodium diet or concomitant diuretics.

BUN/Serum Creatinine: Transient elevations of BUN or serum creatinine especially in volume or salt depleted patients or those with renovascular hypertension may occur. Rapid reduction of longstanding or markedly elevated blood pressure can result in decreases in the glomerular filtration rate and, in turn, lead to increases in BUN or serum creatinine.

Hematologic: A positive ANA has been reported.

Liver Function Tests: Elevations of liver transaminases, alkaline phosphatase, and serum bilirubin have occurred.

10 OVERDOSAGE

Correction of hypotension would be of primary concern. Volume expansion with an intravenous infusion of normal saline is the treatment of choice for restoration of blood pressure.

While captopril may be removed from the adult circulation by hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril; there is no information concerning exchange transfusion for removing captopril from the general circulation.

11 DESCRIPTION

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

CAPOTEN is designated chemically as 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline [MW 217.29].

Captopril is a white to off-white crystalline powder that may have a slight sulfurous odor; it is soluble in water (approx. 160 mg/mL), methanol, and ethanol and sparingly soluble in chloroform and ethyl acetate.

CAPOTEN is available in potencies of 12.5 mg, 25 mg, 50 mg, and 100 mg as scored tablets for oral administration. Inactive ingredients: microcrystalline cellulose, corn starch, lactose, and stearic acid.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of CAPOTEN has not yet been fully elucidated. Its beneficial effects in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. However, there is no consistent correlation between renin levels and response to the drug. Renin, an enzyme synthesized by the kidneys, is released into the circulation where it acts on a plasma globulin substrate to produce angiotensin I, a relatively inactive decapeptide. Angiotensin I is then converted by angiotensin converting enzyme (ACE) to angiotensin II, a potent endogenous vasoconstrictor substance. Angiotensin II also stimulates aldosterone secretion from the adrenal cortex, thereby contributing to sodium and fluid retention.

CAPOTEN prevents the conversion of angiotensin I to angiotensin II by inhibition of ACE, a peptidyldipeptide carboxy hydrolase. This inhibition has been demonstrated in both healthy human subjects and in animals by showing that the elevation of blood pressure caused by exogenously administered angiotensin I was attenuated or abolished by captopril. In animal studies, captopril did not alter the pressor responses to a number of other agents, including angiotensin II and norepinephrine, indicating specificity of action.

ACE is identical to "bradykininase," and CAPOTEN may also interfere with the degradation of the vasodepressor peptide, bradykinin. Increased concentrations of bradykinin or prostaglandin E^2 may also have a role in the therapeutic effect of CAPOTEN .

Inhibition of ACE results in decreased plasma angiotensin II and increased plasma renin activity (PRA), the latter resulting from loss of negative feedback on renin release caused by reduction in angiotensin II. The reduction of angiotensin II leads to decreased aldosterone secretion, and, as a result, small increases in serum potassium may occur along with sodium and fluid loss.

The antihypertensive effects persist for a longer period of time than does demonstrable inhibition of circulating ACE. It is not known whether the ACE present in vascular endothelium is inhibited longer than the ACE in circulating blood.

12.2 Pharmacodynamics

Administration of CAPOTEN results in a reduction of peripheral arterial resistance in hypertensive patients with either no change, or an increase, in cardiac output. There is an increase in renal blood flow following administration of CAPOTEN and glomerular filtration rate is usually unchanged.

Reductions of blood pressure are usually maximal 60 to 90 minutes after oral administration of an individual dose of CAPOTEN. The duration of effect is dose related. The reduction in blood pressure may be progressive, so to achieve maximal therapeutic effects, several weeks of therapy may be required. The blood pressure lowering effects of captopril and thiazide-type diuretics are additive. In contrast, captopril and beta-blockers have a less than additive effect.

Blood pressure is lowered to about the same extent in both standing and supine positions. Orthostatic effects and tachycardia are infrequent but may occur in volume depleted patients. Abrupt withdrawal of CAPOTEN has not been associated with a rapid increase in blood pressure.

12.3 Pharmacokinetics

After oral administration of therapeutic doses of CAPOTEN, rapid absorption occurs with peak blood levels at about one hour. The presence of food in the gastrointestinal tract reduces absorption by about 30 to 40 percent; captopril therefore should be given one hour before meals. Based on carbon-14 labeling, average minimal absorption is approximately 75 percent. In a 24-hour period, over 95 percent of the absorbed dose is eliminated in the urine; 40 to 50 percent is unchanged drug; most of the remainder is the disulfide dimer of captopril and captopril-cysteine disulfide.

Approximately 25 to 30 percent of the circulating drug is bound to plasma proteins. The apparent elimination half-life for total radioactivity in blood is probably less than 3 hours. An accurate determination of half-life of unchanged captopril is not, at present, possible, but it is probably less than 2 hours. In patients with renal impairment, however, retention of captopril occurs (see DOSAGE AND ADMINISTRATION (2.6)).

Studies in rats and cats indicate that CAPOTEN does not cross the blood-brain barrier to any significant extent.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. The high dose in these studies is 150 times the maximum recommended human dose of 450 mg, assuming a 50-kg subject. On a body-surface-area basis, the high doses for mice and rats are 13 and 26 times the maximum recommended human dose, respectively.

Studies in rats have revealed no impairment of fertility.

13.2 Animal Toxicology

Chronic oral toxicity studies were conducted in rats (2 years), dogs (47 weeks; 1 year), mice (2 years), and monkeys (1 year). Significant drug-related toxicity included effects on hematopoiesis, renal toxicity, erosion/ulceration of the stomach, and variation of retinal blood vessels.

Reductions in hemoglobin and/or hematocrit values were seen in mice, rats, and monkeys at doses 50 to 150 times the maximum recommended human dose (MRHD) of 450 mg, assuming a 50-mg subject. On a body-surface-area, these doses are 5 to 25 times maximum recommended human dose (MRHD). Anemia, leukopenia, thrombocytopenia, and bone marrow suppression occurred in dogs at doses 8 to 30 times MRHD on a body-weight basis (4 to 15 times MRHD on a surface-area basis). The reductions in hemoglobin and hematocrit values in rats and mice were only significant at 1 year and returned to normal with continued dosing by the end of the study. Marked anemia was seen at all dose levels (8 to 30 times MRHD) in dogs, whereas moderate to marked leukopenia was noted only at 15 and 30 times MRHD and thrombocytopenia at 30 times MRHD. The anemia could be reversed upon discontinuation of dosing. Bone marrow suppression occurred to a varying degree, being associated only with dogs that died or were sacrificed in a moribund condition in the 1 year study. However, in the 47-week study at a dose 30 times MRHD, bone marrow suppression was found to be reversible upon continued drug administration.

Captopril caused hyperplasia of the juxtaglomerular apparatus of the kidneys in mice and rats at doses 7 to 200 times MRHD on a body-weight basis (0.6 to 35 times MRHD on a surface-area basis); in monkeys at 20 to 60 times MRHD on a body-weight basis (7 to 20 times MRHD on a surface-area

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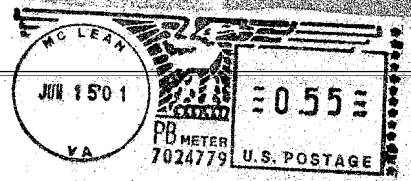

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