CAPOTEN® TABLETS
Captopril

DESCRIPTION
CAPOTEN (captopril) is an inhibitor of angiotensin converting enzyme (ACE), which converts angiotensin I to angiotensin II a potent endogenous vasoconstrictor substance **CAPOTEN** (captopril) is available in potencies of 25 mg and 50 mg, as scored tablets for oral administration. Inactive ingredients: microcrystalline cellulose, corn starch, lactose, and stearic acid.

CLINICAL PHARMACOLOGY
Mechanism of Action:
The mechanism of action of **CAPOTEN** (captopril) 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 resulting in decreased serum concentrations of angiotensin II and aldosterone. However, there is no consistent correlation between renin levels and response to the drug. 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.
ACE is identical to bradykininase " and captopril may also interfere with the degradation of bradykinin, which increases the concentration of bradykinin or prostaglandin E2. This could explain the lack of a consistent correlation between renin levels and response to drug.

Pharmacokinetics
CAPOTEN (captopril) is rapidly absorbed from the gastrointestinal tract; the peak blood level occur at about one hour. The average minimal absorption is approximately 75 percent. The presence of food in the gastrointestinal tract reduces absorption by about 30 to 40 percent. Approximately 25 to 30 percent of the circulating drug is bound to plasma proteins. The apparent elimination half-life in blood is probably less than 3 hours.
Greater than 95 percent of the absorbed dose is eliminated in the urine; 40 to 50 percent is unchanged drug and the remainder are metabolites (disulfide dimer of captopril and captopril-cysteine disulfide). Impaired renal function could result in drug accumulation.
Studies in animals indicate that **CAPOTEN** (captopril) does not cross the blood-brain barrier to any significant extent.

Pharmacodynamics
CAPOTEN (captopril) reduces 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** (captopril) 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** (captopril). 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 effect. 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.
In patients with heart failure, significantly decreased peripheral (systemic vascular) resistance and blood pressure (afterload), reduced pulmonary capillary wedge pressure (preload) and pulmonary vascular resistance, increased cardiac output, and increased exercise tolerance time (ETT) have been demonstrated. These hemodynamic and clinical effects occur after the first dose and appear to persist for the duration of therapy. Clinical improvement has been observed in some patients where acute hemodynamic effects were minimal.

Clinical Trials:
Captopril improved long-term survival and clinical outcome compared to placebo among 2,231 patients with myocardial infarclion (MI) who participated in the Survival and Ventricular Enlargement (SAVE) trial. For inclusion in the study -- a randomized, double-blind, placebo -controlled, multicenter trial--patients (age 21-79 years) had to demonstrate left ventricular dysfunction (ejection fraction ≤ 40%) without overt heart failure. Specifically, captopril reduced the following: all cause mortality (risk reduction =19%, P = 0.022); cardiovascular death (risk reduction= 21%, P = 0.017); manifestations of heart failure requiring initiation or augmentation of digitalis and diuretics (risk reduction =19%, P = 0.008) or requiring the use of ACE inhibitor therapy (risk reduction =35%, P< 0.001); hospitalization for heart failure (risk reduction= 20%, P = 0.034); clinical recurrent MI (risk reduction =25%, P =0.011); and coronary revascularization procedures [coronary artery bypass graft surgery (CABG) and percutaneous transluminal coronary angioplasty (PTCA)] (risk reduction = 24%, P = 0.014).
The cardioprotective effects of captopril observed in subgroups such as those analyzed by age, sex, site of infarction,or ejection fraction were consistent with the overall treatment effects. Captopril provided improvement in survival and clinical outcome even when added to other post-myocardial infarction therapies, such as thrombolytics beta blockers or aspirin.
Potential mechanisms by which captopril improves survival and clinical outcome in patients following myocardial infarction include: attenuation of the progressive left ventricular dilatation and deterioration in left ventricular function; and inhibition of neurohumoral activation.
In a multicenter, double-blind, placebo-controlled trial among 409 patients with insulin-dependent diabetes mellitus and proteinuria with or without hypertension (conventional antihypertensive agents were allowed to achieve blood pressure control), captopril treatment provided a 51% risk reduction in doubling of serum creatinine (P ≤ 0.01), and a 51% risk reduction for the combined morbidity/mortality endpoint of end-stage renal disease (dialysis or renal transplantation) or death (P≤ 0.01).
The effects of treatment with captopril on the preservation of renal function are in addition to any benefit that may have been derived from the reduction in blood pressure. In patients with diabetes mellitus and microalbuminuria, captopril reduced albumin excretion rate and attenuated the decline in glomerular filtration rate during two years of treatment.

INDICATIONS AND USAGE
Hypertension: CAPOTEN (captopril) is indicated for the treatment of hypertension. Captopril 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.
Heart Failure: CAPOTEN (captopril) is indicated in the treatment of congestive heart failure. Although the beneficial effect of captopril in heart failure does not require the presence of digitalis, most controlled clinical trial experience with captopril has been in patients receiving digitalis, as well as diuretic treatment.
Myocardial Infarction: CAPOTEN (captopril) is indicated following myocardial infarction in clinically stable patients with asymptomatic and symptomatic left ventricular dysfunction to improve survival, delay the onset of symptomatic heart failure, reduce hospitalizations for heart failure, and reduce recurrent myocardial Infarction and coronary revascularization procedures.
Diabetic Nephropathy: CAPOTEN (captopril) is indicated for the treatment of diabetic nephropathy (N.B.,'renal disease,due to diabetes mellitus' may be substituted for "diabetic nephropathy"); In these patients, captopril prevents the progression of renal disease and reduces associated clinical sequelae (dialysis,renal transplantation and

death).

CONTRAINDICATIONS

CAPOTEN 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).

WARNINGS

Anaphylactoid and Possibly Related Reactions:

Presumably because angiotensin-converting enzyme is essential for degradation of endogenous bradykinin, patients receiving ACE inhibitors, including captopril, are subject to a variety of adverse reactions to produce effects ranging from relatively mild, such as cough (see PRECAUTIONS), to serious such as the following:

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.

Anaphylactoid reactions during desensitization: Two patients undergoing desensitizing treatment with hymenoptera venom while receiving another ACE inhibitor, enalapril, sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when the ACE inhibitor was temporarily withheld, but they reappeared upon inadvertent rechallenge. Therefore, caution should be used in patients treated with ACE inhibitors undergoing such desensitizations procedures.

Anaphylactoid reactions during high-flux dialysis / lipoprotein apheresis membrane exposure: Anaphylactoid reactions have been reported in patients hemodialyzed with high-flux dialysis membranes. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of medication.

Neutropenia / Agranulocytosis:

The risk of neutropenia is dependent on the clinical status of the patient. Neutropenia is very rare (< 0.02%) in patients with hypertension who have normal renal function (Cr_s < 1.6 mg/dL and no collagen vascular disease).

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 0.2%, 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 patients with renal failure, use of allopurinol concomitantly with captopril has been associated with neutropenia.

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 post-marketing experience. About half of the reported cases had serum creatinine > 2 mg/dL and more than half had collagen vascular disease also receiving procainamide. In heart failure, it appears that the same risk factors (i.e., impaired renal function, etc.) for neutropenia are present.

The neutropenia has usually been prevalent 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.

Patients with complicating factors 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/mm^3) the physician should withdraw captopril and closely follow the patient's course.

Proteinuria:

Total urinary proteins greater than 1 g per day were seen in about 0.7 percent of patients receiving captopril. About 20 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. 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.

In a multicenter, double-blind, placebo-controlled trial in 207 patients with diabetic nephropathy and proteinuria (≥ 500 mg per day) receiving captopril at 75 mg/day for a median of 2 years, there was a consistent reduction in proteinuria. It is unknown whether long-term therapy in patients with other types of renal disease would have similar effects.

Patients with prior renal disease or those receiving captopril at doses greater than 150 mg per day should have urinary protein determinations (dip-stick on first morning urine) prior to treatment, and periodically thereafter.

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.

In hypertension, the possibility of hypotensive effects with the initial doses of captopril can be minimized by either discontinuing the diuretic or increasing the salt intake approximately one week prior to initiation of treatment with CAPOTEN (captopril) or initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, medical supervision should be provided for at least one hour after the initial dose. A transient hypotensive response is not a contraindication to further doses which can be given without difficulty once the blood pressure has increased.

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 dose 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 mg or 12.5 mg bid or 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. 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.

Fetal / Neonatal Morbidity and Mortality:

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.

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Over 100 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 **CAPOTEN** 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 mother 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, **CAPOTEN** 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 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 incidence of cardiovascular 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.

Hepatic Failure:

Rarely, ACE inhibitors have been associated with 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 elevation of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

PRECAUTIONS

General:

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.

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 (e.g., heparin).

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.

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 generate much afterload reduction as others.

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.

Information for Patient:

Patients should be advised to immediately report to their physician any signs or symptoms suggesting angioedema (e.g., swelling of face, eyes, lips, tongue, larynx and extremities, difficulty in swallowing or breathing, hoarseness) and to discontinue therapy. (See WARNINGS).

Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) that does not respond promptly to standard therapy, which may be a sign of neutropenia, or of progressive edema which might be related to proteinuria and nephrotic syndrome.

All patients should be cautioned that excessive perspiration and dehydration may lead to excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Patients should be advised not to use potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes without consulting their physician.

Patients should be warned against interruption or discontinuation of medication unless instructed by the physician.

Heart failure patients on captopril therapy should be cautioned against rapid increases in physical activity.

Patients should be informed that **CAPOTEN** (captopril) should be taken one hour before meals.

Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors,and that these consequences do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. Women should be instructed to notify their physician immediately if pregnancy is suspected.

Drug Interactions:

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 restrictions or dialysis, may occasionally experience a precipitous reduction of blood pressure usually within the first hour after receiving the initial dose of captopril.

Agents Having Vasodilator Activity: Nitroglycerin or other nitrates or other drugs having vasodilator activity should be administered cautiously, and a lower dosage considered.

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

Agents Affecting Sympathetic Activity: The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving ACE inhibitors 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.

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.

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.

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 co-administered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, this may further increase the risk of lithium toxicity.

Drug / Laboratory Test Interaction:

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

Carcinogenesis, Mutagenesis and Impairment of Fertility:

Two-years studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Categories C (first trimester) and D (second and third trimester): See WARNINGS: Fetal/Neonatal Morbidity and Mortality

Nursing Mothers:

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** to the mother.

Pediatric Use:

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

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

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 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 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 photosensitivity, have also been reported. Flushing or pallor has been reported in ≥ 0.5% of patients.

Cardiovascular: Hypotension, tachycardia, chest pain, and palpitations have each been observed in approximately 1% of patients. Angina pectoris. Myocardial infarction, Raynaud's syndrome, and congestive heart failure have each occurred in ≤ 0.3% of patients.

Gastrointestinal: Approximately 2 to 4% (depending on renal status and dose) of patients developed dysgeusia. 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.

Hematologic: Anemia, thrombocytopenia, pancytopenia, and neutropenia/agranulocytosis have been reported.

Immunologic: Angioedema has been reported in approximately 0.1% of patients. Angioedema involving the upper airways has caused fatal airway obstruction.

Respiratory: Cough has been reported in 0.5 - 2% of patients treated with captopril in clinical trials.

Renal: Renal insufficiency, renal failure, nephrotic syndrome, polyuria, oliguria, and urinary frequency have been reported rarely (≤ 0.2%) and are of uncertain relationship to drug use. Proteinuria (See WARNINGS).

The following have been reported in about 0.5 - 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.

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 hepatic 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: The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, and death (see WARNINGS).

Altered Laboratory Findings:

Serum Electrolytes: Hyperkalemia. especially in patients with renal impairment. 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.

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.

DOSAGE AND ADMINISTRATION

CAPOTEN (captopril) should be taken one hour before meals. Dosage must be individualized.
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** (captopril) is 50 mg once daily or 25 mg bid. If satisfactory reduction of blood pressure has not been achieved after one or two weeks the dose may be increased to 100 mg daily in one or two divided doses. Concomitant sodium restriction may be beneficial when **CAPOTEN** is used alone.
If the blood pressure has not been satisfactorily controlled after one to two weeks at this dose, (and the patient is not 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 WARNINGS), with dosage and titration of **CAPOTEN** as noted above.
If further blood pressure reduction is required, the dose may be increased incrementally while continuing the diuretic. A bid dosage schedule may be considered. The dose of **CAPOTEN** in hypertension usually does not exceed 150 mg/day. 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 PRECAUTIONS [Drug Interactions]), but the effects of the two drugs are less than additive.
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 mg bid or tid, or of 12.5 mg bid or tid, may minimize the magnitude or duration of the hypotensive effect (See WARNINGS, Hypotension). 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 bid or tid. After a dose of 50 mg bid or 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 a daily dose of 150 mg or less. A maximum daily dose of 450 mg of **CAPOTEN** (captopril) 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.
Myocardial Infarction: Therapy may be initiated as early as three days following a myocardial infarction. After an initial dose of 6.25 mg, captopril therapy should be increased to 37.5 mg daily in divided doses as tolerated. Captopril should then be increased as tolerated to 75 mg a day in divided doses during the next several days and to a final target dose of 150 mg daily in divided doses over the next several weeks.
If symptomatic hypotension occurs, a dosage reduction may be required. Subsequent attempts at achieving the target dose of 150 mg should be based on the patient's tolerance to captopril.
Captopril may be used in patients treated with other post-myocardial infarction therapies, e.g., thrombolytics, aspirin, beta blockers.
Diabetic Nephropathy: In patients with diabetic nephropathy, the recommended daily dose of captopril is 75 to 100 mg in divided doses. If further blood pressure reduction is required, other antihypertensive agents such as diuretics, beta adrenoceptor blockers, centrally acting agents or vasodilators may be used in conjunction with captopril.
Dosage Adjustment In Renal Impairment: Captopril in divided doses of 75 to 100 mg/day was well tolerated in patients with diabetic nephropathy and mild to moderate renal impairment (See PRECAUTIONS-General, Hyperkalemia). Because **CAPOTEN** (captopril) 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.
Initially, for patients with significant renal impairment, initial daily dosage of **CAPOTEN** (captopril) should be reduced, and smaller increments utilized for titration, which should be quite slow (one-to two-weeks 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.

HOW SUPPLIED

Boxes of 3 strips x 10 tablets of 25 mg.
Boxes of 3 strips x 10 tablets of 150 mg.

All captopril tablets are white and may exhibit a slight sulfurous odor.

STORAGE

Do not store above 25°C.

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