starting CAPOTEN. If resumed during CAPOTEN therapy, such agents should be administered cautiously, and perhaps at lower dosage.

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.

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.

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 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.

Cardiac Glycosides: In a study of young healthy male subjects no evidence of a direct pharmacokinetic captopril-digoxin interaction could be found.

Loop Diuretics: Furosemide administered concurrently with captopril does not alter the pharmacokinetics of captopril in renally impaired hypertensive patients.

Allopurinol: In a study of healthy male volunteers no significant pharmacokinetic interaction occurred when captopril and allopurinol were administered concomitantly for 6 days.

Drug/Laboratory Test Interaction

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

Carcinogenesis, Mutagenesis, 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.

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-kg subject. On a body-surface-area basis, these doses are 5 to 25 times maximum recommended 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 basis); and in dogs at 30 times MRHD on a body-weight basis (15 times MRHD on a surface-area basis).

Gastric erosions/ulcerations were increased in incidence in male rats at 20 to 200 times MRHD on a body-weight basis (3.5 and 35 times MRHD on a surface-area basis); in dogs at 30 times MRHD on a body-weight basis (15 times on MRHD on a surface-area basis); and in monkeys at 65 times MRHD on a body-weight basis (20 times MRHD on a surface-area basis). Rabbits developed gastric and intestinal ulcers when given oral doses approximately 30 times MRHD on a body-weight basis (10 times MRHD on surface-area basis) for only 5 to 7 days.

In the two-year rat study, irreversible and progressive variations in the caliber of retinal vessels (focal sacculations and constrictions) occurred at all dose levels (7 to 200 times MRHD) on a body-weight basis; 1 to 35 times MRHD on a surface-area basis in a dose-related fashion. The effect was first observed in the 88th week of dosing, with a progressively increased incidence thereafter, even after cessation of dosing.

Pregnancy Categories C (first trimester) and D (second and third trimesters)

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. (See **PRECAUTIONS: Pediatric Use**.)

Pediatric Use

Safety and effectiveness in pediatric patients 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 should be used in pediatric patients only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS

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

Renal: About one of 100 patients developed proteinuria (see **WARNINGS**).

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**). 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 photosensitivity, have also been reported.

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

Cardiovascular: Hypotension may occur; see **WARNINGS** and **PRECAUTIONS** [**Drug Interactions**] 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 **WARNINGS: Head and Neck Angioedema, Intestinal Angioedema** and **PRECAUTIONS: Information for Patients**.)

Cough: Cough has been reported in 0.5–2% of patients treated with captopril in clinical trials (see **PRECAUTIONS: General**, Cough).

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: Anaphylactoid and possible related reactions** and **PRECAUTIONS: Hemodialysis).**

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: Fetal/Neonatal Morbidity and Mortality.

Altered Laboratory Findings

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

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 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 tablets, USP) is 25 mg b.i.d. or t.i.d. If satisfactory reduction of blood pressure has not been achieved after one or two weeks, the dose may be increased to 50 mg b.i.d. or t.i.d. Concomitant sodium restriction may be beneficial when CAPOTEN is used alone.

The dose of CAPOTEN in hypertension usually does not exceed 50 mg t.i.d. 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 **WARNINGS** and **PRECAUTIONS: Drug Interactions** regarding hypotension), 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 b.i.d. or t.i.d. and then, if necessary, to 150 mg b.i.d. or t.i.d. (while continuing the diuretic). The usual dose range is 25 to 150 mg b.i.d. or t.i.d. 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 b.i.d. or t.i.d., 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 or 12.5 mg t.i.d. 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 t.i.d. After a dose of 50 mg t.i.d. 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 t.i.d. 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.

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 t.i.d.

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 t.i.d. CAPOTEN should then be increased to 25 mg t.i.d. during the next several days and to a target dose of 50 mg t.i.d. over the next several weeks as tolerated (see **CLINICAL PHARMACOLOGY**).

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

Diabetic Nephropathy: The recommended dose of CAPOTEN for long term use to treat diabetic nephropathy is 25 mg t.i.d.

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.

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 **WARNINGS: Anaphylactoid reactions during membrane exposure** and **PRECAUTIONS: Hemodialysis**.)

HOW SUPPLIED

CAPOTEN® (Captopril Tablets, USP)

12.5 mg tablets in bottles of 100 (NDC 49884-793-01), **25 mg tablets** in bottles of 100 (NDC 49884-794-01) and 1000 (NDC 49884-794-10), **50 mg tablets** in bottles of 100 (NDC 49884-795-01) and 1000 (NDC 49884-795-10), and **100 mg tablets** in bottles of 100 (NDC 49884-796-01). Bottles contain a desiccant-charcoal canister.

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 30° C (86° F). Keep bottles tightly closed (protect from moisture).

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