

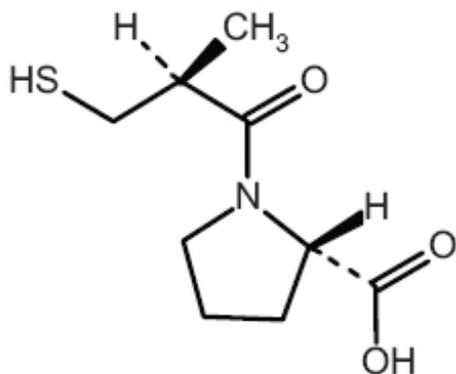
**CAPTOPRIL- captopril tablet**  
**Bryant Ranch Prepack**

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**CAPTOPRIL TABLETS, USP**

**DESCRIPTION**

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

Captopril is designated chemically as 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline. Molecular formula C<sub>9</sub>H<sub>15</sub>NO<sub>3</sub>S [MW 217.29] and has the following structural formula: 9153



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.

Each scored tablet, for oral administration, contains 12.5 mg, 25 mg, 50 mg or 100 mg of captopril. In addition, each tablet contains the following inactive ingredients: microcrystalline cellulose, corn starch, anhydrous lactose, colloidal silicon dioxide, talc and palmitic acid.

**CLINICAL PHARMACOLOGY**

**Mechanism of Action**

The mechanism of action of 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. 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.

Captopril prevents the conversion of angiotensin I to angiotensin II by inhibition of ACE, a peptidyl dipeptide 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 captopril may also interfere with the degradation of the vasodepressor peptide, bradykinin. Increased concentrations of bradykinin or prostaglandin E<sub>2</sub> may also have a role in the therapeutic effect of Captopril.

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.

### **Pharmacokinetics**

After oral administration of therapeutic doses of captopril, 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**

### **Pharmacodynamics**

Administration of captopril 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 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 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. 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 captopril 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. Placebo controlled studies of 12 weeks duration in patients who did not respond adequately to diuretics and digitalis show no tolerance to beneficial effects on ETT; open studies, with exposure up to 18 months in some cases, also indicate that ETT benefit is maintained.

Clinical improvement has been observed in some patients where acute hemodynamic effects were minimal.

The Survival and Ventricular Enlargement (SAVE) study was a multicenter, randomized, double-blind, placebo-controlled trial conducted in 2,231 patients (age 21-79 years) who survived the acute phase of a myocardial infarction and did not have active ischemia. Patients had left ventricular dysfunction (LVD), defined as a resting left ventricular ejection fraction <40%, but at the time of randomization

were not sufficiently symptomatic to require ACE inhibitor therapy for heart failure. About half of the patients had symptoms of heart failure in the past. Patients were given a test dose of 6.25 mg oral captopril tablets and were randomized within 3-16 days post infarction to receive either captopril tablets or placebo in addition to conventional therapy. Captopril tablets were initiated at 6.25 mg or 12.5 mg tid and after two weeks titrated to a target maintenance dose of 50 mg tid. About 80% of patients were receiving the target dose at the end of the study. Patients were followed for a minimum of two years and for up to five years, with an average follow-up of 3.5 years.

Baseline blood pressure was 113/70 mm Hg and 112/70 mm Hg for the placebo and captopril tablets groups, respectively. Blood pressure increased slightly in both treatment groups during the study and was somewhat lower in the captopril tablets group (119/74 Vs. 125/77 mm Hg at 1 yr).

Therapy with captopril tablets improved long-term survival and clinical outcomes compared to placebo. The risk reduction for all cause mortality was 19% (P=0.02) and for cardiovascular death was 21% (P=0.014). Captopril treated subjects had 22% (P=0.034) fewer first hospitalizations for heart failure. Compared to placebo, 22% fewer patients receiving captopril developed symptoms of overt heart failure. There was no significant difference between groups in total hospitalizations for all cause (2056 placebo; 2036 captopril).

Captopril tablets were well tolerated in the presence of other therapies such as aspirin, beta blockers, nitrates, vasodilators, calcium antagonists and diuretics.

In a multicenter, double-blind, placebo controlled trial, 409 patients, age 18-49 of either gender, with or without hypertension, with type I (juvenile type, onset before age 30) insulin-dependent diabetes mellitus, retinopathy, proteinuria > 500 mg per day and serum creatinine < 2.5 mg/dL, were randomized to placebo or Captopril tablets (25 mg tid) and followed for up to 4.8 years (median 3 years). To achieve blood pressure control, additional antihypertensive agents (diuretics, beta blockers, centrally acting agents or vasodilators) were added as needed for patients in both groups.

The Captopril tablets group had a 51% reduction in risk of doubling of serum creatinine (P<0.01) and a 51% reduction in risk for the combined endpoint of end-stage renal disease (dialysis or transplantation) or death (P<0.01). Captopril tablets treatment resulted in a 30% reduction in urine prote in excretion within the first 3 months (P<0.05), which was maintained throughout the trial. The Captopril tablets group had somewhat better blood pressure control than the placebo group, but the effects of Captopril tablet on renal function were greater than would be expected from the group differences in blood pressure reduction alone. Captopril tablets were well tolerated in this patient population.

In two multicenter, double-blind, placebo controlled studies, a total of 235 normotensive patients with insulin-dependent diabetes mellitus, retinopathy and microalbuminuria (20-200 mcg/min) were randomized to placebo or Captopril tablets (50 mg bid) and followed for up to 2 years. Captopril tablets delayed the progression to overt nephropathy (proteinuria > 500 mg/day) in both studies (risk reduction 67% to 76%; P<0.05). Captopril tablets also reduced the albumin excretion rate. However, the long term clinical benefit of reducing the progression from microalbuminuria to proteinuria has not been established.

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

## INDICATIONS AND USAGE

Captopril tablets USP are indicated for the treatment of hypertension. **Hypertension :**

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

## WARNINGS

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.

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.

Captopril tablets are 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. **Heart Failure :**

Captopril tablets are 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. **Left Ventricular Dysfunction After Myocardial Infarction :**

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

In considering use of captopril tablets, it should be noted that in controlled trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks. In addition, ACE inhibitors (for which adequate data are available) cause a higher rate of angioedema in black than in non-black patients (see ). **: WARNINGS Angioedema**

## CONTRAINDICATIONS

Captopril tablets are 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

### 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.

#### See . , , : **CLINICAL PHARMACOLOGY DOSAGE AND ADMINISTRATION ADVERSE REACTIONS Altered Laboratory Findings**

: 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 .) **Hyperkalemia: and ; : PRECAUTIONS**  
**Information for Patients**  
**Drug Interactions**  
**ADVERSE REACTIONS**  
**Altered Laboratory Findings**

: Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.  
*Cough*

: 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.  
*Valvular Stenosis*

: 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.  
*Surgery/Anesthesia*

### **Information for Patients**

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**  
**Angioedema**

Patients should be told to report promptly any indication of infection (e.g., sore throat, fever), which may be a sign on 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 an 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. (See .) : **and ;**  
**PRECAUTIONS**  
**General**  
**Drug Interactions**  
**ADVERSE REACTIONS**

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 captopril tablets USP should be taken one hour before meals (see ).

### **DOSAGE AND ADMINISTRATION**

Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

### **Pregnancy.**

### **Drug Interactions**

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.  
*Hypotension*

### - Patients on Diuretic Therapy :

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 captopril tablets USP 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.

Data on the effect of concomitant use of other vasodilators in patients receiving captopril 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 captopril. If resumed during captopril tablet therapy, such agents should be administered cautiously, and perhaps at lower dosage. *Agents Having Vasodilator Activity :*

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 Causing Renin Release :*

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. Betaadrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. *Agents Affecting Sympathetic Activity :*

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. *Agents Increasing Serum Potassium :*

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. *Inhibitors Of Endogenous Prostaglandin Synthesis :*

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. *Lithium :*

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

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

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

### **Drug/Laboratory Test Interactions**

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 human dose (MRHD). Anemia, leukopenia, thrombocytopenia, and bone marrow suppression occurred in dogs at doses 8 to 30 times MRHD on a bodyweight 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 a 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 : .**  
**WARNINGSFetal/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 captopril tablet to the mother. (See ) : . **PRECAUTIONSPediatric 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.

Captopril tablets 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.

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

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. *Dermatologic* :

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

Hypotension may occur; see for discussion of hypotension with captopril therapy. *Cardiovascular* : **and** : **WARNINGS PRECAUTIONS Drug Interactions**

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.

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. *Dysgeusia* :

Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been reported in approximately one in 1000 patients. *Angioedema* :

Angioedema involving the upper airways has caused fatal airway obstruction. (See and .) :

**WARNINGS Angioedema: PRECAUTIONS Information for Patients**

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

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.

Anaphylactoid reactions (see and ). *Body as a whole* :: **WARNINGS Anaphylactoid and Possibly Related Reactions: PRECAUTIONS Hemodialysis**

Asthenia, gynecomastia. *General* :

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

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

Pancreatitis, glossitis, dyspepsia. *Gastrointestinal* :

Anemia, including aplastic and hemolytic. *Hematologic* :

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

Symptomatic hyponatremia. *Metabolic* :

Myalgia, myasthenia. *Musculoskeletal* :

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

Bronchospasm, eosinophilic pneumonitis, rhinitis. *Respiratory* :

Blurred vision. *Special Senses* :

Impotence. *Urogenital* :

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.

## 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

Captopril tablets should be taken one hour before meals. Dosage must be individualized.

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 captopril. **Hypertension**

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The initial dose of captopril tablets USP 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 captopril is used alone.

The dose of captopril 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 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 captopril is being started in a patient already receiving a diuretic, captopril therapy should be initiated under close medical supervision (see and regarding hypotension), with dosage and titration of captopril as noted above. **WARNINGS: PRECAUTIONS**  
**Drug Interactions**

If further blood pressure reduction is required, the dose of captopril 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 captopril 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 captopril 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 captopril 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 captopril 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 captopril therapy (see ), but the effects of the two drugs are less than additive. : **PRECAUTIONS Drug Interactions**

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 ); for these patients, titration to the usual daily dosage can then occur within the next several days. **Heart Failure - : WARNINGS Hypotension**

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 captopril should not be exceeded.

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

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

Therapy may be initiated as early as three days following a myocardial infarction. After a single dose of 6.25 mg, captopril tablets therapy should be initiated at 12.5 mg tid. Captopril tablets 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**

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

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

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

Because captopril is excreted primarily by the kidneys, excretion rates are reduced in patients with impaired renal function. **Dosage Adjustment in Renal Impairment -**

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

## Captopril 50 mg Tablet

### CAPTOPRIL

captopril tablet

#### Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:63629-2541(NDC:64679-904)
<b>Route of Administration</b>	ORAL		

#### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
CAPTOPRIL (UNII: 9G64RSX1XD) (CAPTOPRIL - UNII:9G64RSX1XD)	CAPTOPRIL	50 mg

#### Inactive Ingredients

Ingredient Name	Strength
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D6 1U)	
STARCH, CORN (UNII: O8232NY3SJ)	
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
TALC (UNII: 7SEV7J4R1U)	
PALMITIC ACID (UNII: 2V16EO95H1)	

## Product Characteristics

<b>Color</b>	WHITE	<b>Score</b>	2 pieces
<b>Shape</b>	ROUND	<b>Size</b>	11mm
<b>Flavor</b>		<b>Imprint Code</b>	W;904
<b>Contains</b>			

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63629-2541-1	60 in 1 BOTTLE		
2	NDC:63629-2541-2	30 in 1 BOTTLE		
3	NDC:63629-2541-3	90 in 1 BOTTLE		
4	NDC:63629-2541-4	120 in 1 BOTTLE		

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA074532	09/11/2009	

**Labeler** - Bryant Ranch Prepack (171714327)

**Registrant** - Bryant Ranch Prepack (171714327)

## Establishment

Name	Address	ID/FEI	Business Operations
Bryant Ranch Prepack		171714327	REPACK(63629-2541) , RELABEL(63629-2541)

Revised: 10/2012

Bryant Ranch Prepack