

PACKAGE INSERT TEMPLATE FOR CAPTOPRIL TABLET

Brand or Product Name

[Product name] Tablet 50mg

[Product name] Tablet 25mg

[Product name] Tablet 12.5mg

Name and Strength of Active Substance(s)

Captopril ...mg

Product Description

[Visual description of the appearance of the product (eg colour, markings etc)]

eg White, circular flat beveled edge tablets marked '50' on one side

Pharmacodynamics

Captopril is an oral antihypertensive agent that inhibits angiotensin-converting enzymes (ACE), thus preventing conversion of angiotensin I to angiotensin II, which is a potent vasoconstrictor and stimulator of aldosterone secretion (aldosterone suppression reduces sodium and water retention).

It exerts its effect in hypertension and heart failure by suppressing the renin-angiotensin system. ACE inhibitors also prevent the breakdown of bradykinin (a potent vasodilator). The net result is vasodilatation, decreased peripheral vascular resistance, decreased blood pressure, increased cardiac output, and a relative increase in renal, cerebral, and coronary blood flow

Pharmacokinetics

Absorption

- Approximately 60% to 75% of a dose of captopril is absorbed from the gastrointestinal tract
- Peak plasma concentrations occur within about an hour.
- Effect of food: reduces absorption by about 30% to 40%

Distribution

- Protein binding: approximately 25% to 30%
- Protein binding decreases with decreasing renal function
- Volume of Distribution: 0.7 L/kg
- It crosses the placenta and is found in breast milk at about 1% of maternal blood concentrations

Metabolism

- About 50% of a Captopril dose is metabolized to inactive metabolites; captopril-cysteine disulfide

Excretion

- It is largely excreted in the urine (more than 95%), where by 40 to 50% as unchanged drug, the rest as disulfide and other metabolites.
- Captopril is removed by haemodialysis.
- The elimination half-life has been reported to be 2 to 3 hours but this is increased in renal impairment.

Indication

Hypertension in adult patients. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

The blood pressure lowering effects of Captopril and thiazides are additive.

Treatment of patients with heart failure who have not responded adequately to treatment with diuretics and digitalis

Treatment of myocardial infarction

Treatment of diabetic nephropathy

Recommended Dosage

**Captopril should be taken before meals*

**Dosage should be individualized*

Hypertension: Initial dose: 50mg once daily or 25mg twice daily. If satisfactory reduction of blood pressure has not been achieved after 1 or 2 weeks, the dose may be increased to 100mg daily in 1 or 2 divided doses. If the blood pressure has not been satisfactorily controlled after 1-2 weeks at this dose (and the patient is not already receiving a diuretic). A modest dose of a thiazide-type diuretic (eg: hydrochlorothiazide, 25mg daily), should be added.

If further blood pressure reduction is required, the dose may be increased incrementally while continuing the diuretic and a 3 times daily dosage schedule may be considered. The dose in hypertension usually not exceed 150mg/day. A maximum daily dose 450mg should not be exceeded.

Heart failure: In patients with either normal or low blood pressure, who has been vigorously treated with diuretics who may be hyponatremic and/or hypovolemic, a starting dose of 6.25mg or 12.5mg 3 times daily may minimize the magnitude or duration of the hypotensive effect. For these patients, titrate to the usual daily dosage within the next several days.

For most patients the usual daily dosage is 25mg 3 times daily. After a dose 50mg 3 times daily is reached further increased in dosage should be delayed, where possible for at least 2 weeks to determine if a satisfactory response occurs. Most patients had a satisfactory improvement at 50 or 100mg 3 times daily. A maximum daily dose of 450mg should not be exceeded.

Myocardial Infarction: Greater efficacy is achieved if therapy initiated after > 3 days following a myocardial infarction. The initial dose is 6.25mg therapy should be increased to 37.5mg daily in divided doses as tolerated. Captopril should then be increased as tolerated to 75mg a day in divided doses during the next several days to a final target dose of 150mg daily in divided doses over the next several weeks.

Diabetic Nephropathy: Recommended daily dose: 75-100mg in divided doses.

Dosage Adjustment in Renal Impairment: Captopril in divided doses of 75-100mg/day was tolerated. For patients with significant renal impairment. Initial daily dosage should be reduced and smaller increments utilized for titration over 1 to 2 weeks intervals. After the desired therapeutic effect has been achieved, the dose should be slowly back-titrated to determine the minimal effective dose.

Mode of Administration

Oral

Contraindications

A history of previous hypersensitivity to Captopril or any other angiotensin-converting enzyme inhibitor (eg: a patient who has experienced angioedema during therapy with any other ACE inhibitor.)

Warnings and Precautions

[Specific package insert requirement for ACE Inhibitors]

INCREASED RISK OF BIRTH DEFECTS, FOETAL AND NEONATAL MORBIDITY AND DEATH WHEN USED THROUGHOUT PREGNANCY

General: Impaired Renal Function:

Some patients with renal diseases particularly those with bilateral renal artery stenosis, have developed increase in BUN and serum creatinine after reduction of blood pressure with Captopril, usually along with a diuretic. Captopril dosage reduction or discontinuation of diuretic, or both maybe required. For some of these patients, it may not be possible to normalize blood pressure and maintain adequate renal perfusion. Some patients with heart failure have experienced reduction in renal function during long-term treatment that usually stabilized at the reduced level. A few patients have developed angioedema of the face, mucous membrane of the mouth and the extremities which is reversible upon discontinuation of the drug. Laryngeal edema has also been reported.

Valvular stenosis: Captopril, as with any drug that reduces vascular resistance, should be used only with extreme caution in patients with aortic stenosis because of the potentially harmful consequence of reduced coronary perfusion secondary to reduced blood pressure.

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 of 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 (eg: heparin)

Cough: Cough has been reported with the use of ACE inhibitors. The cough is nonproductive, persistent and resolves after discontinuation of therapy.

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.

Patients should be advised to their physician any signs and symptoms suggesting **angioedema** (eg, swelling of face, eyes, lips, tongue, larynx and extremities, difficulty in swallowing or breathing, hoarseness), and to discontinue therapy. Patient should be told to report promptly any indication of infection (eg, sore throat, fever) that does not respond promptly to standard therapy which may be 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: vomiting or diarrhea, may also lead to fall in blood pressure; patients should be advised to consult with physician.

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

Patients should be informed that Captopril should be taken 1hr before meals.

Captopril may cause a false positive urine test for acetone.

Use in Children: Safety and effectiveness in children have not been established.

WARNINGS

Proteinuria has been seen < 1% of patient receiving Captopril, but this has been predominantly in patients had prior renal diseases. Although membranous glomerulopathy in biopsies taken from some proteinuric patients, or received relatively high doses of Captopril (in excess of 150mg/day). or both. For patients with prior renal diseases or those receiving Captopril at doses > 150 mg/day should have urinary protein estimations (dipstick on first morning urine) prior to treatment and periodically thereafter.

Neutropenia has occurred in some patients in the clinical studies within 3 months after Captopril has been started, especially for those who has preexisting impaired renal function collagen vascular disease, or who are receiving immunosuppressant therapy, the while blood cell and differential counts should be performed prior to therapy, every 2 weeks during the first 3 months of Captopril therapy and periodically thereafter.

If the neutrophil count falls below 1000/mm³. Captopril should be discontinued and the patient course should be followed. All patients receiving Captopril should be told to report any sign of infection (eg: sore throat. fever). Serious infections resulting from neutropenia and which proved fatal in a few occurred only in patients with impaired renal function.

Hypotension: Excessive hypotension was rarely seen in hypertensive patients but is a possible consequence of Captopril use in salt-/volume depleted patients (eg. those treated vigorously with diuretics), patients with heart failure or those patients undergoing 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 1 week prior to initiation of treatment with Captopril, or initiating of therapy with small doses (6.25 or 12.5mg). Medical supervision should be provided for at least 1 hr after the initial dose.

In patients with heart failure exaggerated hypotensive have been occurred usually within 1 hr of the initial dose of Captopril. This transient fall in pressure may occur after any of the first several doses and is usually well tolerated, producing either no symptoms or brief mild lightheadedness, although in rare instances it has been associated with arrhythmia or conduction defects.

Because of the potential fail in blood pressure in these patients, therapy should be started under very close medical supervision. A starting dose 6.25 or 12.5mg twice or 3 times daily may minimize the hypotensive effect.

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

Interactions with Other Medicaments

Diuretics

Patients on diuretics, 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 and may occasionally experience dizziness or light headedness, usually mild, indicative of hypotension usually within the first hour after receiving the initial dose of captopril.

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 which contain potassium should also be used with caution.

Agent Having Vasodilator Activity

Nitroglycerin or other nitrates or other drugs having vasodilator activity should be administered cautiously and a lower dosage considered.

Other antihypertensive agents

Captopril has been safely co-administered with other commonly used antihypertensive agents (e.g. beta blockers and long acting calcium channel blockers). Concomitant use of these agents may increase the hypotensive effects of captopril. Treatment with nitroglycerine and other nitrates, or other vasodilators, should be used with caution.

Agent Causing Renin Release

Captopril's effect will be augmented by antihypertensive agents that cause renin release, eg: diuretics (eg, thiazides) which may activate the renin-angiotensin-aldosterone system.

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs (including Indomethacin) and ACE inhibitors exert an additive effect on the increase in serum potassium, whereas renal function may decrease. In principle, these effects are reversible. In rare cases, acute renal failure may occur, particularly in patients with compromised renal function such as the elderly or dehydrated. Antihypertensive effect of an ACE inhibitor may reduce with chronic administration of NSAIDs. Concomitant use should be avoided.

Statement on Usage During Pregnancy and Lactation

[Specific package insert requirement for ACE Inhibitors]

INCREASED RISK OF BIRTH DEFECTS, FOETAL AND NEONATAL MORBIDITY AND DEATH WHEN USED THROUGHOUT PREGNANCY

Pregnancy

When used in pregnancy during the 2nd and 3rd trimesters, ACE inhibitors can cause injury and even death to the developing fetus. Captopril should be avoided in those planning pregnancy, and discontinued as soon as possible when pregnancy is detected. They should only be used in pregnant women where the expected benefit clearly outweighs the risk.

Lactation

Captopril has been detected in human breast milk at concentrations of approximately 1% of maternal blood levels. Due to a potential for serious adverse reactions in the nursing infant, consider discontinuation of either breastfeeding or captopril, taking into account the importance of the drug to the mother

Adverse Effects / Undesirable Effects

Skin: rash, pruritus, pemphigoid-like lesion, photosensitivity, exacerbation of psoriasis, Stevens-Johnson Syndrome

Gastrointestinal: Disorder of taste, intestinal angioedema, nausea, diarrhoea, stomatitis resembling aphthous ulcers

Renal: Proteinuria. Renal insufficiency, renal failure, nephrotic syndrome. polyuria, oliguria and urinary frequency have been reported

Altered laboratory findings: Serum electrolytes: Hyperkalemia, especially in patients with renal impairment. Hyponatremia, particularly in patients receiving a low sodium diet or concomitant diuretics. Transient elevation of BUN and creatinine especially in volume or salt depleted patients or those with renovascular hypertension.

Hepatic: Hepatotoxicity

Hematologic: Neutropenia/agranulocytosis, anemia, thrombocytopenia and pancytopenia

Cardiovascular: hypotension, tachycardia, chest pain, palpitations, angina pectoris, myocardial infarction, Raynaud's syndrome, congestive heart failure

Immunologic: angioedema , anaphylactoid reaction

Respiratory: cough , bronchospasm

Surgery/Anesthesia: In patients undergoing major surgery, or during anesthesia Captopril may cause hypotension.

Others: paresthesias of the hands, serum sickness, lymphadenopathy

Overdose and Treatment

Symptoms: Severe hypotension, bradycardia, circulatory shock, electrolyte imbalances, renal failure.

Treatment: The main adverse effect is hypotension which usually responds to supportive treatment and volume expansion. Volume expansion with an I. V. infusion of normal saline is the choice for normalization of the blood pressure.

Storage Conditions

[eg Store below.... °C]

Dosage Forms and Packaging Available

[Packaging type & pack size]

Name and Address of Manufacturer

[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder

[Name & full address of marketing authorization holder]

Date of Revision of Package Insert

[day/month/year]