

New Zealand Data Sheet

m-Captopril

Captopril 12.5mg, 25mg, 50mg and 100mg tablet USP

Presentation

m-Captopril 12.5mg tablets are white to off-white, round flat tablets with beveled edges with W over 902 debossed on one surface and break line on the other.

m-Captopril 25mg tablets are white to off-white, round flat tablets with beveled edges with W over 903 debossed on one surface and cross line on the other.

m-Captopril 50mg tablets are white to off-white, round flat tablets with beveled edges with W over 904 debossed on one surface and break line on the other.

m-Captopril 100mg tablets are white to off-white, round flat tablets with beveled edges with W over 905 debossed on one surface and break line on the other.

Uses

Actions

Captopril is a sulfhydryl-containing angiotensin-converting enzyme (ACE) inhibitor used in the treatment of hypertension and heart failure.

Although its exact mode of action is not fully elucidated, most of the beneficial effects appear to result from suppression of the renin-angiotensin-aldosterone system. However since it also effectively reduces blood pressure in patients with low renin concentrations other mechanisms are probably also involved.

The formation of angiotensin I is mediated by renin, an enzyme released into the circulation by the kidneys in response to a low circulating blood volume or blood pressure.

Captopril prevents the conversion of angiotensin I, to angiotensin II by competing for the angiotensin-converting enzyme (ACE). Reduction of angiotensin II results in decreased aldosterone secretion which results in sodium and fluid loss together with small increases in serum potassium. Additional effects of captopril on bradykinin and prostaglandins are also postulated.

The hypotensive effect of captopril persists for a longer of time than inhibition of ACE in the blood. It is not known whether ACE present in vascular endothelium is inhibited longer than ACE in circulating blood.

Administration of captopril increases the renal blood flow with glomerular filtration rate typically remaining unchanged.

In **hypertensive patients**, captopril reduces blood pressure by decreasing total peripheral resistance, with either no change or an increase in cardiac output. Orthostatic hypotension and tachycardia are infrequent but may occur in volume-depleted patients. Peak blood pressure reductions usually occur within 1 to 2 hours of an oral dose being administered. The reduction in blood pressure may be gradual, and several weeks of therapy may be required before maximal therapeutic effects are achieved. Abrupt withdrawal of captopril has not been associated with a rapid increase in blood pressure.

In patients with **heart failure** captopril decreases systemic vascular resistance (afterload), reduces pulmonary capillary wedge pressure (preload) and pulmonary vascular resistance, and increases cardiac output (stroke index) and exercise tolerance time.

In patients who have survived **myocardial infarction**, captopril reduces left ventricular remodelling which is a recognised precursor of symptomatic heart failure.

Captopril is of benefit to patients with **diabetic nephropathy** independent of whether they are hypertensive or suffer from insulin-dependent or non-insulin-dependent diabetes mellitus. Treatment of hypertension in such patients would be expected to slow the rate of loss of renal function, but captopril demonstrates a proteinuric effect independent of any hypertensive effect. Captopril may also impede the development of microalbuminuria in early diabetic nephropathy.

Pharmacokinetics

Approximately 60-75% of an oral dose of captopril is absorbed from the GI tract, with peak plasma levels reached within about one hour. Food can decrease absorption by 25-40%. Captopril is 25-30% bound to plasma proteins and is widely distributed throughout the body except the CNS. The terminal phase volume of distribution (2L/kg) suggests that captopril is distributed into deep tissues. Captopril crosses the placenta and is found in breast milk at about 1% of maternal blood concentrations. The half-life of unchanged medicine in patients with normal renal function is less than 2 hours, and the duration of action is approximately 2-6 hours; this may be prolonged in patients on high doses and in patients with decreased renal function.

Captopril is extensively metabolised with the major metabolite being captopril dimer SQ 14,551. In vitro studies have demonstrated that SQ 14,551 is significantly less active than captopril as an ACE inhibitor. Captopril is excreted mainly in the urine with 40-50% excreted as the unchanged medicine and 35% as metabolites (captopril dimer and conjugates with endogenous thiol compounds e.g. captopril-cysteine. In vitro studies suggest that the metabolites are labile and in vivo interconversions may occur. Renal excretion of unchanged captopril occurs principally via tubular secretion.

Indications

Hypertension:

Captopril can be used as monotherapy or as a component of a multiple-medicine regimen in the stepped-care approach. The blood pressure lowering effects of captopril and thiazide diuretics are additive.

Heart Failure:

Captopril is indicated for patients with heart failure who have not responded adequately to, or cannot be controlled by, conventional therapy e.g. diuretics, +/- digoxin.

Myocardial Infarction:

Improved survival and reduced fatal and non-fatal cardiovascular events have been found in patients given captopril with asymptomatic and symptomatic left ventricular dysfunction.

Diabetic Nephropathy:

Captopril is indicated for the treatment of diabetic nephropathy in Type 1 diabetes. The rate of progression of renal disease and the development of serious adverse clinical outcomes (death, renal transplant or dialysis) is decreased.

Dosage and Administration

Dosages must be individualised, and medication is maximally absorbed if taken **one hour before meals**.

Adults:

Hypertension:

Before starting therapy using captopril, consideration should be given to recent antihypertensive treatment, the degree of elevation of the blood pressure, salt restriction and any other clinical circumstances. Ideally, discontinue the patient's previous antihypertensive therapy one week before starting captopril. If this is not possible, diuretic use should be continued.

The initial dose of captopril is 50mg once daily or 25mg twice daily. If a satisfactory reduction in blood pressure has not been achieved after 1 to 2 weeks the dose may be increased and administered in divided doses. If blood pressure requires further reduction after 2 weeks of therapy at this higher dosage, a small daily dose of a thiazide diuretic may be added. The diuretic dose may be increased at 1 to 2 week intervals if required until its highest usual antihypertensive dose is reached. If this is still insufficient, the dose of captopril may be increased further. Most people with mild to moderate hypertension are well controlled on doses of captopril of up to 100mg daily. For patients with severe hypertension, the dose may be increased incrementally, with the maximum daily dose not exceeding 450mg.

Captopril therapy should be initiated under close medical supervision where there is a risk of inducing severe first dose hypotension due to the patient being either volume depleted or already on diuretics or other antihypertensive medications. The initial dose of captopril should be reduced and administered at night before going to bed.

For patients with accelerated or malignant hypertension, the captopril dosage may be increased every 24 hours under continuous medical supervision until either a satisfactory response or the maximum dosage is reached. Use of a higher potency diuretic e.g. frusemide may be required. When captopril is used as monotherapy, concomitant salt restriction may be beneficial. Other antihypertensives may be used in conjunction with captopril.

Heart failure:

Before starting therapy consideration should be given to recent diuretic therapy and the possibility of severe salt/volume depletion. In patients who are normo-or hypotensive and who may be hyponatremic and/or hypovolemic a starting dose of 6.25 or 12.5mg twice daily may reduce any hypotensive effect. Therapy with captopril must be started under close medical supervision and should be added to treatment with diuretic (and digitalis where indicated).

The usual starting dose is 25mg twice daily. If necessary, the dose may be increased gradually up to 50mg three times daily. The usual maximum dose is 150mg per day but this may be increased at the discretion of the physician. The daily maximum should not exceed 450mg.

Myocardial Infarction:

Captopril is used prophylactically in clinically stable patients with symptomatic or asymptomatic left ventricular dysfunction. Therapy may be started 3 days after a myocardial infarction with an initial dose of 6.25mg of captopril, increasing over several weeks to 150mg daily in divided doses if tolerated. It may be used in

conjunction with other post-myocardial infarction therapies e.g. beta-blockers.

Diabetic Nephropathy:

75 to 100mg may be given daily in divided doses. Other antihypertensive therapies may be used with captopril if further reduction in blood pressure is required. In patients with severe renal impairment, the initial dose of captopril should be reduced to 12.5mg twice daily and if a diuretic is required a loop diuretic e.g. frusemide should be the diuretic of choice.

Use in Renal Dysfunction:

Captopril is excreted primarily by the kidneys and therefore either smaller doses or less frequent dosing may be required.

Creatinine Clearance (CrCl)(ml/min/1.73m)	Maximum Total Daily Dose (mg)
80 – 41	300
40 – 21	150
20 – 11	75
<10	37.5

Children

Experience with captopril in children is limited and it should only be used if other methods for controlling blood pressure have not been effective.

The initial dose of captopril is 0.3mg/kg under close medical supervision. This may be halved in infants, and in older children on diuretics, who are more prone to initial hypotension. If further reduction of blood pressure is required, each single dose can be increased weekly in increments to 0.6, 1.2, and 2.0mg/kg. Concomitant diuretic therapy has additive effects. For patients with malignant hypertension, doses can be increased daily. The maximum total daily dose is 6mg/kg.

Contraindications

Hypersensitivity to any component of the medication

Pregnancy

History of angioedema

Warnings and Precautions

Dual blockade of the renin-angiotensin-aldosterone system:

As a consequence of inhibiting the renin-angiotensin-aldosterone system, hypotension, syncope, hyperkalaemia, and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system. Dual blockade of the renin-angiotensin-aldosterone system (e.g. by adding an ACE-inhibitor to an angiotensin II receptor antagonist) is therefore not recommended in patients with already controlled blood pressure and should be limited to individually defined cases with close monitoring of renal function.

Anaphylactoid Reactions:

Anaphylactoid reactions have occurred in patients undergoing desensitisation treatment with hymenoptera venom while receiving an ACE inhibitor. Caution should be used in patients treated with ACE inhibitors undergoing desensitisation procedures. Patients haemodialysed with high-flux polyacrylonitrile membranes are likely to experience anaphylactoid reactions if they are treated with ACE inhibitors. Anaphylactoid reactions have also been reported in patients undergoing low-density

lipoprotein apheresis with dextran sulphate absorption. These combinations should be avoided.

Angioedema:

Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been observed. If angioedema involving the tongue, glottis or larynx occurs, airway obstruction may occur and be fatal. Prompt treatment including subcutaneous administration of epinephrine 1:1000 is essential. Swelling confined to the face, mucous membranes, lips and extremities usually resolves with discontinuation of captopril.

Aortic stenosis:

Captopril should be used with caution because of the potential consequences of reduced coronary perfusion secondary to the reduced blood pressure.

Heart failure:

Some patients with heart failure may also experience deterioration in renal function during long term therapy. A lower dose is all that is usually required.

Cough:

ACE inhibitor induced cough should be considered as part of the differential diagnosis of cough.

Hyperkalaemia:

Small increases in serum potassium concentration may occur secondary to captopril-induced decreases in aldosterone secretion, especially in patients with impaired renal function. Potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other medicines associated with increases in serum potassium should be used with caution.

Hypotension:

Transient hypotension may occur at the start of therapy, particularly in patients with congestive heart failure and in sodium- or volume-depleted patients. Therapy should be started as small doses, under close medical supervision (see Dosage and Administration).

Impaired hepatic function:

Patients with liver dysfunction may be prone to reversible cholestatic and mixed cholestatic-hepatocellular jaundice. Associated symptoms include pruritis, malaise, fever, anorexia and eosinophilia.

Impaired renal function:

Captopril should be used with caution in patients with impaired renal function, especially those with bilateral renal-artery stenosis, or with renal artery stenosis of a solitary kidney. Some patients 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.

Neutropenia/Agranulocytosis:

Neutropenia has occurred almost exclusively in patients with pre-existing renal dysfunction; collagen vascular disease (e.g. systemic lupus erythematosus and scleroderma); or receiving immunosuppressant therapy. These high-risk patients should have white blood cell and differential counts performed prior to therapy and every 2 weeks during the first 3 months of captopril therapy. In addition, all patients should be told to report signs of infection such as sore throat and fever. If the neutrophil count falls below $1000/\text{mm}^3$, captopril should be discontinued; rechallenge can occur once the count is normal.

Proteinuria:

Proteinuria has occurred mainly in patients with existing renal disease or those receiving daily doses > 150mg with some patients developing nephrotic syndrome. In most cases, proteinuria subsided or cleared regardless of whether or not captopril was continued. At-risk groups should have urinary protein estimations at monthly intervals for the first 9 months. Parameters such as BUN and serum creatinine were seldom altered in patients with proteinuria. In patients without prior renal disease and taking daily doses < 150mg, the incidence of proteinuria is 0.2%.

Surgery/Anaesthesia:

Captopril may aggravate any hypotension caused during the procedure(s), as it blocks angiotensin II formation secondary to compensatory renin release. This can be corrected by volume expansion.

Urine acetone:

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

Use in Pregnancy and Lactation**Use in pregnancy:**

Category D.

Captopril should be discontinued and alternative therapy instigated as soon as possible once pregnancy has been detected. It appears that adverse effects do not result from intra-uterine exposure to captopril if that exposure is limited to the first trimester of pregnancy. However the use of captopril during the second and third trimesters of pregnancy has been associated with foetal and neonatal injury including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure and death. Oligohydramnios has also been reported, presumably due to decreased renal function: oligohydramnios in this setting has been associated with foetal limb contractures, craniofacial deformation and hypoplastic lung development. Prematurity and patent ductus arteriosus have also been reported although it is unclear whether these occurrences were due to captopril exposure.

Use in nursing mothers:

Use in breastfeeding is not recommended in the first few weeks after delivery because of the possibility of profound neonatal hypotension; preterm babies may be at particular risk. Use may be considered when the infant is older if an ACE inhibitor is necessary for the mother; careful follow-up of the infant for possible signs of hypotension is recommended.

Use in Children

Safety and effectiveness in children have not been established. There is limited experience with the use of captopril in children with the dosage generally being reported as being either comparable to or less than (on a weight basis) the adult dose. Infants especially newborns may be more susceptible to the adverse haemodynamic effects of captopril. Excessive, prolonged and unpredictable decreases in blood pressure and associated complications including oliguria and seizures have been reported. Because renal function in infants is not equivalent to that of older children and adults lower doses of captopril should be used with the patients under close medical supervision. Captopril should only be used in children if other measures for controlling blood pressure have not been effective.

Adverse Effects

Captopril is generally well tolerated at doses below 150mg daily.

Skin:

A dose related rash has occurred in 7% of patients at doses 150mg or less, but is more frequent at higher doses or in patients with renal dysfunction. The rash is usually pruritic and maculopapular but rarely urticarial, and generally occurs in the first 4 weeks of therapy. The rash is reversible on reduction of dosage and a short course of antihistamine, or on discontinuation of medicine. Eosinophilia, pruritis and fever may accompany the rash in 7-10% of patients. Pruritis, flushing, a reversible pemphigoid-like lesion, photosensitivity and angioedema have also been reported.

Renal:

Proteinuria (1% incidence); and/or transient increases in BUN and serum creatinine (see Warnings and Precautions). Renal insufficiency, renal failure, polyuria, oliguria and urinary frequency have been reported in 0.1 to 0.2% of patients but are of uncertain relationship to medicine dose. Cases of nephrotic syndrome and glomerulopathy have also been reported.

Haematological:

Neutropenia and/or agranulocytosis (see Warnings and Precautions). Cases of reversible lymphadenopathy, anaemia, thrombocytopenia, and pancytopenia have been reported.

Hepatic:

Rare cases of hepatocellular injury and jaundice. Transient elevation of liver enzyme levels (see Warnings and Precautions).

Angioedema:

Involving the extremities, face, lips mucous membranes, tongue, glottis or larynx has been reported in 0.1% of patients (see Warnings and Precautions). Serum sickness and bronchospasm have been reported.

Cardiovascular:

Hypotension on initiating captopril therapy (see Dosage and Administration). Tachycardia, chest pain and palpitations have also been reported (1%). Angina pectoris, myocardial infarction, Raynaud's Syndrome, congestive heart failure, flushing or pallor have all been reported at incidences of 0.2 to 0.5%.

Alteration in taste:

A diminution or loss of taste perception is reported in 2% of patients receiving 150mg or less of captopril and in 7% of patients receiving doses in excess of 150mg. This is reversible and usually self-limiting (2 to 3 months) even with continued therapy. There may be associated weight loss.

Gastrointestinal:

The following have been reported in about 0.5 to 2% of patients: gastric irritation, abdominal pain, nausea, vomiting, diarrhoea, anorexia, constipation, and dyspepsia.

Central Nervous System:

Low incidences of dizziness, headache, malaise, fatigue, insomnia and paresthesia have been reported. Also reported have been ataxia, confusion, depression, nervousness and somnolence.

Others:

As with other ACE Inhibitors, a persistent dry cough has been reported as has a

syndrome which is usually reversible, comprising of fever, myalgia, arthralgia, rash, eosinophilia and an elevated ESR. Rarely reported are dry mouth, dyspnoea, alopecia, impotence, loss of libido, disturbed vision and itching and/or dry eyes.

Clinical adverse effects which have been reported but for which an incidence or causal relationship has not been determined include:

General: Asthenia, gynecomastia.

Cardiovascular: Cardiac arrest, cerebrovascular accident, syncope.

Dermatologic: bullous pemphigus, Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, glossitis

Haematologic: aplastic and haemolytic anaemia.

Hepatobiliary: hepatitis including rare cases necrosis, cholestasis.

Metabolic: symptomatic hyponatremia.

Musculoskeletal: myalgia, myasthenia.

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

Respiratory: bronchospasm, eosinophilic pneumonitis, rhinitis.

Special senses: blurred vision.

Interactions

Diuretics: Some patients, especially those in whom diuretic therapy has recently been initiated, may experience a precipitous fall in blood pressure after the first dose of captopril (see Warnings and Precautions). If feasible, the diuretic should be discontinued for a week prior to captopril's introduction or initiating therapy with small doses (6.25 or 12.5mg). Alternatively, close medical supervision is required for at least an hour after the first dose.

Agents having Vasodilator Activity:

Data on the concomitant use of other vasodilators with captopril are not available and the use of nitro-glycerine or other nitrates (as used for the management of angina) or other vasodilators should be approached with caution with the possibility of a lower dose being considered.

Agents causing Renin Release:

Captopril's effect will be augmented by hypertensive agents that cause renin release e.g. thiazidediuretics 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 either alone or in conjunction with diuretics. Agents affecting sympathetic activity e.g. ganglionic or adrenergic neuron blocking agents should be used with caution. While beta-adrenergic blocking agents add further antihypertensive effect to captopril the overall response is less than additive. In heart failure, special caution is necessary because sympathetic stimulation is a vital component supporting circulatory function and inhibition with beta-blockade carries a potential hazard of further depressing myocardial contractility.

Agents increasing serum potassium:

Potassium supplements or potassium-sparing diuretics e.g. spironolactone, triamterene and amiloride should only be given for documented hypokalaemia, as a significant increase of serum potassium may occur. Salt substitutes containing potassium should be used with caution.

Inhibitors of Endogenous Prostaglandin Synthesis:

Indomethacin may reduce the antihypertensive effect of captopril, especially in cases of low renin hypertension. Other non-steroidal anti-inflammatory agents may also

have this effect.

Lithium:

ACE inhibitors when used concomitantly with lithium therapy have been reported as increasing serum lithium levels and symptoms of lithium toxicity may occur. If a diuretic is also used, the risk of lithium toxicity is further increased. Frequent monitoring of serum lithium levels is recommended.

Betablockers:

The blood lowering effects of captopril and betablockers are less than additive.

Allopurinol:

In patients with renal failure the use of captopril concomitantly with allopurinol has been associated with neutropenia.

Procainamide:

In patients with heart failure the use of procainamide concomitantly with captopril has been associated with neutropenia.

Laboratory Test Results:

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

Elevations of hepatic transaminases, alkaline phosphatase and serum bilirubin have occurred.

A transient elevation of BUN and serum creatinine may occur especially in patients who are volume depleted or have renovascular hypertension. In instances of rapid reduction of long standing or severely elevated blood pressure the glomerular filtration rate may decrease transiently also resulting in transient rises in serum creatinine and BUN.

Small increases in the serum potassium concentration frequently occur especially in patients with renal impairment.

Hyponatraemia may occur particularly in patients on a low salt diet or receiving concomitant diuretics.

Changes in blood cell counts and anaemia have occurred during treatment with captopril.

Overdosage

In the event of overdosage, correction of hypotension would be of primary concern. Volume expansion with an intravenous infusion of normal saline, whilst the patient is in the supine position is the treatment of choice for restoration of blood pressure. Captopril may be removed from adult circulation by haemodialysis but there are inadequate data concerning the effectiveness of haemodialysis for removing captopril from the circulation of neonates or children.

Pharmaceutical Precautions

Store below 25°C Protect from heat, light and moisture.

Medicine Classification

Prescription Medicine.

Package Quantities

Plastic HDPE bottles containing 100, 500 and 1000 tablets.

(Not all strengths and pack sizes are marketed)

Further Information

Tablets contain lactose.

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