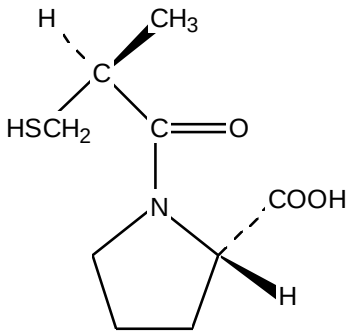
PRODUCT INFORMATION
CAPTOPRIL SANDOZ® 12.5MG, 25MG & 50MG TABLETS

NAME OF THE MEDICINE

Chemical name: 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline

Generic name: Captopril

Chemical Structure:



CAS: 62571-86-2

DESCRIPTION

Captopril is the first of a new chemical class of antihypertensive agents. It also has been shown to be of benefit in the management of heart failure.

It is a white or almost white crystalline powder; and is soluble in water, chloroform, dichloromethane, and ethanol (96%). It is a highly specific competitive inhibitor of angiotensin I converting enzyme, the enzyme responsible for the conversion of angiotensin I to angiotensin II

In addition to captopril, Captopril Sandoz tablets contain microcrystalline cellulose, maize starch, lactose, stearic acid.

PHARMACOLOGY

Captopril is an ACE inhibitor.

Mechanism of action

The mechanism of action of captopril has not yet been fully elucidated, however its beneficial effects in hypertension and heart failure appear to result primarily through suppression of the renin-angiotensin-aldosterone system. However, there is not

consistent correlation between renin levels and response to the drug. Renin, an enzyme synthesised 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 enzymatically by angiotensin converting enzyme (ACE) to the octapeptide angiotensin II, one of the most potent endogenous vasoconstrictor substances. Angiotensin II also stimulates aldosterone secretion from the adrenal cortex thereby contributing to sodium and fluid retention and potassium loss.

Captopril prevents the conversion of angiotensin I to angiotensin II by inhibition of ACE, a peptidyldipeptide carboxyhydrolase. This is reflected by a decrease in the pressor substance angiotensin II, and an increase in plasma renin activity (PRA). The latter is due to the relative lack of negative feedback on renin release caused by reduction in angiotensin II. Decreased concentrations of aldosterone are found in blood and urine and, as a result small increases in serum potassium may occur along with sodium and fluid loss.

ACE is identical to bradykininase, and captopril may also interfere with the degradation of the vasopressor peptide bradykinin. Increased concentrations of bradykinin or prostaglandin E2 may also have a role in the therapeutic effect of captopril.

Pharmacodynamics
Administration of captopril results in a reduction in peripheral arterial resistance in hypertensive patients with either no change or an increase in cardiac output. Clinically significant reductions of blood pressure are often observed 60 to 90 minutes after oral administration of captopril. However, the reduction in blood pressure is usually progressive and to achieve maximal therapeutic effects of a given dosage regimen, several weeks of administration may be required. The duration of effect appears to be dose related.

Blood pressure is lowered in both standing and supine positions. Orthostatic effects and tachycardia are infrequent, occurring most commonly in volume depleted patients. No sudden increase in blood pressure after withdrawal of the drug has been observed.

Studies have demonstrated an increase in renal blood flow after administration of captopril. Glomerular filtration rate is usually unchanged. In instances of rapid reduction of long standing or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, resulting in transient rises in serum creatinine and urea nitrogen. In humans, the renin-angiotensin system plays a role in regulating the glomerular filtration rate when renal perfusion is low. Administration of captopril may result in acute deterioration of glomerular filtration in such patients.

Pharmacokinetics
Absorption
Following oral administration of captopril, rapid absorption occurs with peak blood levels of approximately 1 microgram/L being found ½ to 1 hour after a 100mg dose. The average minimal absorption is approximately 75%. The presence of food in the gastrointestinal tract reduces absorption by 25% to 40%. Approximately 30% of the

drug is bound to plasma proteins. The apparent oral bioavailability is increased in patients receiving captopril chronically compared with acute use. It may be possible to reduce the dosage during chronic therapy and still maintain adequate blood pressure control.

Distribution
Captopril appears to be distributed between three compartments in humans. The terminal phase volume of distribution (2L/kg) suggests that captopril is distributed into deep tissues.

Metabolism
Captopril is extensively metabolised. The major metabolite is captopril dimer.

In vitro studies have demonstrated that captopril dimer is significantly less active than captopril as an inhibitor of angiotensin converting enzyme.

Excretion
Captopril and its metabolites (captopril dimer and conjugates with endogenous thiol compounds, eg. captopril-cysteine) are excreted principally in the urine. In vitro studies suggest that the metabolites are labile and that interconversions may occur in vivo. Approximately 40% of an administered dose is excreted unchanged in the urine in 24 hours and 35% as metabolites. Total body clearance is approximately 0.8 L/kg/hour.

The elimination half-life of captopril is 1 to 2 hours and of total radioactivity is approximately 4 hours. The elimination half-life of captopril increases with decreasing renal function; the elimination rate correlates with creatinine clearance. The half-life for non renal elimination is 156 hours. Dosage adjustment is required in patients with renal impairment (See DOSAGE AND ADMINISTRATION).

CLINICAL TRIALS

Captopril improved long term survival and clinical outcome compared to placebo among 2,231 patients with myocardial infarction who participated in the Survival and Ventricular Enlargement (SAVE) trial. For inclusion in the study (a randomised, double-blind, placebo controlled, multicentre trial), patients (aged 21 to 79 years) had to demonstrate left ventricular dysfunction (ejection fraction <40%) without overt heart failure. Specifically, captopril, when given 3-16 days (mean 11 days) after myocardial infarction, reduced the following: all cause mortality (risk reduction 19%, p=0.022); cardiovascular death (risk reduction 21%, p=0.017); manifestations of heart failure requiring initiation or augmentation of digitalis and diuretics (risk reduction 19%, p=0.008) or requiring the use of ACE inhibitor therapy (risk reduction 35%, p<0.001); hospitalisation for heart failure (risk reduction 20%, p=0.034); clinical recurrent myocardial infarction (risk reduction 25%, p=0.011); and coronary revascularisation procedures (coronary artery bypass graft surgery and percutaneous transluminal coronary angioplasty) (risk reduction 24%, p=0.014).

Potential mechanism by which captopril improves survival and clinical outcome in patients following myocardial infarction include attenuation of the progressive left ventricular dilatation and deterioration in left ventricular function, and inhibition of neurohumoral activation.

Heart failure patients treated with captopril demonstrate increases in exercise time, ability to perform at higher workloads, and improvement in functional capabilities by New York Heart Association criteria. Administration of captopril to heart failure patients has resulted in consistent increases in cardiac output, cardiac index and stroke volume index. The effects were accompanied by reductions in systemic vascular resistance, pulmonary vascular resistance, total vascular resistance, pulmonary arterial pressure, pulmonary capillary wedge pressure and right atrial pressure. A consistent fall in mean arterial pressure was generally seen but it rarely became symptomatic. After short-term administration, a slight reduction in heart rate occurred which generally returned to pre-captopril levels with long term therapy. Occasionally, a more marked reduction in heart rate may occur.

In studies involving a small number of patients with heart failure, a reduction in coronary blood flow which correlated with a fall in myocardial oxygen demand has been observed, with simultaneous increases in cardiac index and reduction in systemic vascular resistance.

In a multicentre, double-blind, placebo controlled trial among 409 patients with insulin dependent diabetes mellitus and proteinuria with or without hypertension (conventional antihypertensive agents were allowed to achieve blood pressure control), captopril treatment provided a 51% risk reduction in doubling of serum creatinine ($p \leq 0.01$). The effects of treatment with captopril on the preservation of renal function are in addition to any benefit that may have been derived from the reduction in blood pressure.

In two multicentre, double blind, placebo controlled studies, a total of 235 normotensive patients with insulin dependent diabetes mellitus of 4 to 30 years duration with onset before the age of 39 years, retinopathy, serum creatinine within the normal range and microalbuminuria (albumin excretion rate 20 to 200 microgram/minute) were randomised to placebo or captopril 50 mg twice daily and followed for up to two years. Captopril delayed the progression to overt nephropathy (albumin excretion rate > 200 microgram/minute, i.e. proteinuria greater than or equal to 500 mg/day) in both studies (risk reduction 67 to 76%: $p < 0.05$). However, the long-term clinical benefit of reducing the progression from microalbuminuria to proteinuria has not been established.

INDICATIONS

Hypertension

Captopril Sandoz is indicated for the treatment of hypertension.

In using Captopril Sandoz, consideration should be given to the risk of neutropenia/agranulocytosis (See PRECAUTIONS).

Captopril Sandoz 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.

Myocardial infarction
Captopril Sandoz is 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 hospitalisations for congestive heart failure in these patients. The efficacy data for the use of Captopril Sandoz following myocardial infarction are strongest for initiation of therapy beyond three days post-infarction.

Heart failure
Captopril Sandoz is indicated for the treatment of heart failure. In symptomatic patients it is recommended that Captopril Sandoz be administered together with a diuretic.

Diabetic nephropathy
Captopril Sandoz is indicated for the treatment of diabetic nephropathy (proteinuria > 500mg/day) in patients with type I insulin dependent diabetes mellitus. In these patients Captopril Sandoz reduces the progression of renal disease and reduces associated clinical sequelae (dialysis, renal transplantation and death).

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients or to any other ACE inhibitor.

History of previous hypersensitivity to captopril.

Pregnancy (See PRECAUTIONS, Use in Pregnancy).

Patients with a history of hereditary and/or idiopathic angioedema or angioedema associated with previous treatment with an ACE inhibitor.

Concomitant use of angiotensin-converting enzyme inhibitors (ACEIs) - including captopril - or of angiotensin receptor antagonists (ARBs) with aliskiren in patients with type 2 diabetes.

PRECAUTIONS

Anaphylactoid and possibly related reactions
Presumably because angiotensin converting enzyme is essential for degradation of endogenous bradykinin, patients receiving ACE inhibitors are subject to a variety of adverse reactions producing effects ranging from relatively mild, such as cough (See Precautions), to serious, such as the following:

Head and neck angioedema. Severe life-threatening angioedema has been reported rarely with most of the ACE inhibitors. The overall incidence is approximately 0.1 to 0.2%. There seems to be no sex difference in the incidence of angioedema or in the predisposition to angioedema in patients with heart failure or hypertension. In the majority of reported cases, the symptoms occurred during the first week of therapy, although the onset of angioedema may be delayed for weeks or months. Patients may have multiple episodes of angioedema with long symptom-free intervals. The aetiology is thought to be nonimmunogenic and may be related to accentuated bradykinin activity. Usually the angioedema involves nonpitting oedema of the skin and oedema of the subcutaneous tissues and mucous membranes. Angioedema may occur with or without urticaria.

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with ACE inhibitors. In such cases, the product should be discontinued promptly and appropriate monitoring instituted to ensure complete resolution of symptoms.

In instances when swelling has been confined to the face and lips, the angioedema has generally resolved either without treatment or with antihistamines. Angioedema associated with laryngeal oedema is potentially life-threatening. When involvement of the tongue, glottis or larynx is likely to cause airway obstruction, appropriate therapy including adrenaline and oxygen administration should be carried out promptly or the patient hospitalised. Patients who respond to medical treatment should be observed carefully for a possible re-emergence of symptoms of angioedema.

There are reports where changing the patient over to another ACE inhibitor was followed by recurrence of oedema and others when it was not. Because of the potential severity of this rare event, another ACE inhibitor should not be used in patients with a history of angioedema to a drug of this class. (See CONTRAINDICATIONS).

Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks.

Intestinal angioedema. Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including CT scans or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Patients receiving co-administration of ACE inhibitor and mTOR (mammalian target of rapamycin) inhibitor (e.g., temsirolimus, sirolimus, everolimus) therapy may be at increased risk for angioedema.

Anaphylactoid reactions during desensitisation. Two patients undergoing desensitising treatment with Hymenoptera venom while receiving another ACE

inhibitor, enalapril, sustained life threatening anaphylactoid reactions. In the same patients, these reactions were avoided when the ACE inhibitor was temporarily withheld, but they reappeared upon inadvertent rechallenge. Therefore, caution should be used in patients treated with ACE inhibitors undergoing such desensitisation procedures.

Anaphylactoid reactions during high flux dialysis/lipoprotein apheresis membrane exposure. Patients haemodialysed using high flux polyacrylonitrile ("AN69") membranes are highly likely to experience anaphylactoid reactions if they are treated with ACE inhibitors. Anaphylactoid reactions have also been reported in patients undergoing low density lipoprotein aphaeresis with dextran sulfate absorption. These combinations should therefore be avoided, either by use of a different class of medication or alternative membranes (e.g. cuprophane or polysulfone (PSF) for haemodialysis).

Proteinuria
Total urinary proteins greater than 1 g/day were seen in about 0.7% of patients receiving captopril, the majority of whom had prior renal disease or were receiving relatively high doses (in excess of 150mg/day), or both. In mild to moderate hypersensitive patients the incidence dropped to 0.06%. Alterations in renal function (as assessed by blood area nitrogen and serum creatinine) were infrequent and did not occur in those who had no prior renal disease.

Nephrotic syndrome (hypoalbuminaemia, oedema and proteinuria > 3 g/day) occurred in about one-fifth of the proteinuric patients. In most cases, proteinuria subsided or cleared within six months whether or not captopril was continued. Parameters of renal function such as BUN and creatinine were seldom altered in the patients proteinuria.

Although membranous glomerulopathy was found in biopsies taken from proteinuric patients, a causal relationship to captopril has not been established since pretreatment biopsies were not taken and membranous glomerulopathy has been shown to occur in hypertensive patients not receiving captopril.

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

Patients with prior renal disease or those receiving captopril at doses > 150mg/day should have urinary protein estimations (dipstick on first morning urine) prior to treatment and periodically thereafter.

Neutropenia/agranulocytosis
Neutropenia has occurred in some patients receiving captopril, but this has been limited chiefly to those who had pre-existing impaired renal function, collagen vascular disease, immunosuppressant therapy, or a combination of these complicating factors.

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed.

In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk of neutropenia in clinical trials was about 1 per 500, a frequency over 15 times that for uncomplicated hypertension. Daily doses of captopril were relatively high in these patients, particularly in view of their diminished renal function. In foreign marketing experience in patients with renal failure, use of allopurinol concomitantly with captopril has been associated with neutropenia.

In patients with collagen vascular disease (e.g. systemic lupus erythematosus, scleroderma), particularly those with coexisting renal impairment, captopril should be prescribed only after an assessment of benefit and risk since neutropenia has occurred in 8 out of the 124 such patients in clinical trials.

Neutropenia was noted 2 to 13 weeks after captopril therapy started and it developed relatively slowly, the white cell count falling to its nadir over 10 to 30 days. Neutropenia was usually not associated with significant alterations in red cell or platelet counts.

Evaluation of white cell counts in the total patient population suggests a possible general, but milder, effect on neutrophils. In most studies, there was a 5 to 10 percent decrease in leucocyte count over the first eight weeks of treatment. This was not seen in patients on placebo, propranolol or hydrochlorothiazide, although it was seen on standard triple therapy. The change in white cell count was not progressive and the effect was no longer apparent after 12 weeks in most patients. The significance of these changes is uncertain.

For patients with significantly impaired renal function, collagen vascular disease, or who are receiving immunosuppressant drugs and for patients with pre-existing neutropenia, white blood cell and differential counts should be performed prior to therapy and at regular intervals thereafter.

All patients receiving captopril should be instructed to report any signs of infection (e.g. sore throat, fever). A complete white blood cell count should be performed immediately when such report is made.

In general, neutrophils returned to normal in about two weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of neutropenia cases have ended fatally, but almost all fatalities were in patients with serious illness, i.e. collagen vascular disease, renal failure, heart failure or on immunosuppressant therapy, or a combination of these complicating factors.

Evaluation of the hypertensive or heart failure patient should include assessment of renal function.

If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately two week intervals for three months, then periodically.

Since discontinuation of captopril and other drugs has generally led to prompt return of the white cell count to normal, upon confirmation of neutropenia (neutrophil count <1.000/mm^3), the physician should withdraw captopril and closely follow the patient's course.

Hypotension
Hypotension may occur occasionally in patients commencing treatment with ACE inhibitors. Excessive hypotension is rarely seen in patients with uncomplicated hypertension but can develop in patients with impaired renal function, in those who are salt/volume depleted because of renovascular disease, diuretic therapy, vomiting or diarrhoea, and in patients undergoing dialysis and (See PRECAUTIONS, INTERACTIONS WITH OTHER MEDICINES and ADVERSE EFFECTS).

In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure greater than 20% are recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated producing either no symptoms or mild light headedness, although in rare instances it has been associated with arrhythmia or conduction defects. Hypotension was the reason for discontinuation of drug in 3.6% of patients with heart failure.

Only a few patients with refractory heart failure secondary to a mechanical lesion of the heart have been studied with captopril. Of possible concern in patients with aortic stenosis are the potentially harmful consequences of reduced coronary perfusion secondary to hypotension. Patients treated for severe congestive heart failure should be cautioned to increase their physical activity slowly.

In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed. This may be associated with syncope, neurological deficits, oliguria and/or progressive azotaemia and, rarely, with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started at low doses (6.25 or 12.5 mg twice or three times daily) under very close supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dosage is increased, or diuretic therapy is commenced or increased.

Similar considerations may apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident, respectively. In all high risk patients, it is advisable to initiate treatment at lower dosages than those usually recommended for uncomplicated patients.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be given without

difficultly once the blood pressure has increased. The magnitude of the decrease is greatest early in the course of treatment: this effect stabilises within a week or two, and generally returns to pretreatment levels, without a decrease in therapeutic efficacy, within two months.

Hepatic failure
Rarely, ACE inhibitors have been associated with a syndrome which starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and sometimes death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical attention.

Use with caution under the following circumstances:

Hyperkalaemia
Because the ACE inhibitors decrease the formation of angiotensin II and the subsequent production of aldosterone, serum potassium exceeding 5.5 mEq/L may occur, although frank hyperkalaemia is uncommon. Hyperkalaemia is more likely in patients with some degree of renal impairment, hypoaldosteronism or those treated with potassium sparing diuretics or potassium supplements, and in those consuming potassium containing salt substitutes or other drugs associated with increases in serum potassium (e.g. heparin, cotrimoxazole also known as trimethoprim/sulfamethoxazole). Diabetic patients, and elderly diabetics particularly, may be at increased risk of hyperkalaemia. It is recommended that patients taking an ACE inhibitor should have serum electrolytes (including potassium, sodium and urea) measured from time to time. This is more important in patients taking diuretics.

Cough
A persistent, dry (non-productive) cough has been reported with all of the ACE inhibitors and appears to be a class effect. In studies with various ACE inhibitors, the incidence of cough varies between 2% and 15% depending upon the drug, dosage and duration of use. The cough, which may be due to increased bronchial reactivity, appears to be more common in women (approximately 2:1) and often worse when lying down. It may resolve or diminish with continued use or with dose reduction, but usually returns on rechallenge. The cough is most likely due to stimulation of the pulmonary cough reflex by kinins (bradykinin) and/or prostaglandins, which accumulate because of ACE inhibition. Once a patient has developed intolerable cough, an attempt may be made to switch the patient to another ACE inhibitor, the reaction may recur but this is not invariably the case. A change to another class of drugs may be required in severe cases. No residual effects have been reported. ACE inhibitor induced cough should be considered part of the differential diagnosis of cough.

Use in diabetic nephropathy
In managing a patient with microalbuminuria the physician should be mindful of the importance of reducing other risk factors for progression to proteinuria, for example the need to maintain adequate control of blood glucose and blood pressure.

The physician should also alert normotensive patients with diabetic nephropathy to the possibility of the rare occurrence of hypotension during treatment with captopril.

Surgery/anaesthesia
In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, captopril will block angiotensin II formation secondary to compensatory renin release. This may lead to hypotension, which can be corrected by volume expansion.

Impaired renal function
Hypertension. Some patients with renal disease, particularly those with renal artery stenosis, have developed increases in serum concentrations of BUN and serum creatinine after reduction of blood pressure with captopril, usually in conjunction with a diuretic. Captopril dosage reduction and/or discontinuation of diuretic may be required. For some of these patients, it may not be possible to normalise blood pressure and maintain adequate renal perfusion; therefore titration to acceptable blood pressure may be necessary.

In patients with low renal perfusion (bilateral renal artery stenosis, renal artery stenosis to a solitary kidney) the renin-angiotensin may be an important regulator of glomerular filtration rate. Captopril should be administered cautiously in such patients.

Evaluation of the hypertensive patient should always include assessment of renal function (See DOSAGE AND ADMINISTRATION). If a deterioration in renal function has occurred after treatment with one ACE inhibitor, then it is likely to be precipitated by another and in these patients usage of another class of antihypertensive agent would be preferable. Patients with unilateral renal artery disease present a special problem as deterioration of function may not be apparent from measurement of blood urea nitrogen and serum creatinine.

Heart failure. About 20% of patients develop stable elevations of BUN and serum creatinine greater than 20% above normal or baseline upon long-term treatment with captopril. Less than 5% of patients, generally those with severe pre-existing renal disease, required discontinuation of treatment due to progressively increasing creatinine. Subsequent improvement probably depends upon the severity of the underlying renal disease.

Risk of hypokalaemia
The combination of an ACE inhibitor with a thiazide diuretic does not rule out the occurrence of hypokalaemia. Regular monitoring of potassium should be performed.

Carcinogenesis, mutagenesis, impairment of fertility
Two year studies with doses of 50 to 1,350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential.

Use in pregnancy (Category D)
As with all ACE inhibitors, Captopril Sandoz should not be taken during pregnancy. Pregnancy should be excluded before starting treatment with Captopril Sandoz and avoided during treatment.

If a patient intends to become pregnant, treatment with ACE inhibitors must be discontinued and replaced by another form of treatment.

If a patient becomes pregnant while on ACE inhibitors, she must immediately inform her doctor to discuss a change in medication and further management. Monitoring of the foetal development should be performed on a regular basis.

When used in pregnancy, ACE inhibitors can cause injury and even death to the developing foetus.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with foetal and neonatal injury including hypotension, neonatal skull hypoplasia, anuria, reversible and irreversible renal failure and death.

Oligohydramnios has also been reported, presumably resulting from decreased foetal renal function. Oligohydramnios has been associated with foetal limb contractures, craniofacial deformities, hypoplastic lung development and intrauterine growth retardation. Prematurity and patent ductus arteriosus have been reported.

A historical cohort study in over 29, 000 infants born to non-diabetic mothers has shown 2.7 times higher risk for congenital malformations in infants exposed to any ACE inhibitor during 1st trimester compared to no exposure. The risk ratios for cardiovascular and central nervous system malformations were 3.7 times (95% confidence interval 1.89 to 7.3) and 4.4 times (95% confidence interval 1.37 to 14.02) respectively, compared to no exposure.

Australian categorisation definition of Category D. Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Use in lactation
Following oral administration, concentrations of captopril in human breast milk are 1% or less of those in maternal blood. The effect of this low level of captopril on the breastfed infant has not been determined. Caution should be exercised when captopril is administered to a woman who is breastfeeding and, in general, breastfeeding should be interrupted.

Use in children
Safety and effectiveness in children have not been established, although there is limited experience in children with secondary hypertension and varying degrees of renal failure. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used only if the potential benefit justifies the risk.

INTERACTIONS WITH OTHER MEDICINES

Hypotension in patients on diuretic therapy. When a diuretic is added to the therapy of a patient receiving captopril, the antihypertensive effect is usually additive. Patients receiving diuretics, especially those in whom diuretic therapy was recently instituted or in those with intravascular volume depletion, may sometimes experience an excessive reduction of blood pressure usually within the first hour of therapy with captopril. The possibility of hypotensive effects may be minimised by discontinuing the diuretic and ensuring adequate hydration and salt intake prior to commencing ACE inhibitor therapy. If it is not possible to discontinue the diuretic, the starting dose of captopril should be reduced and the patient closely observed for several hours following the initial dose of the ACE inhibitor and until blood pressure has stabilised.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics. Concomitant use of a renin-angiotensin system inhibiting drug (ACE inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID, including COX-2 inhibitor) and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination, and periodically thereafter.

Dual blockade of the Renin-Angiotensin-System (RAS) with ACEIs, ARBs (angiotensin receptor antagonists) or aliskiren. The concomitant use of ACEIs, including captopril with other agents acting on the RAS is associated with an increased incidence of hypotension, hyperkalemia, and changes in renal function compared to monotherapy. Most patients receiving the combination of two RAS inhibitors do not obtain any additional benefit compared to monotherapy. In general, avoid combined use of RAS inhibitors. It is recommended to monitor blood pressure, renal function and electrolytes in patients on captopril and other agents that affect the RAS. The concomitant use of ACEIs, including captopril, or of ARBs with aliskiren, should be avoided in patients with severe renal impairment (GFR <30 ml/min). The concomitant use of ACEIs, including captopril, or of ARBs with aliskiren is contraindicated in patients with type 2 diabetes.

Lithium. Increased serum lithium and symptoms of lithium toxicity have been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. These drugs should be co-administered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

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. ß-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive, patients will need to be closely supervised.

Agents increasing serum potassium. Since captopril decreases aldosterone production, elevation of serum potassium may occur. Potassium sparing diuretic (e.g. spironolactone, triamterene or amiloride) or potassium supplements should be given only for documented hypokalaemia, and then with caution, since they lead to a significant increase in serum potassium. Salt substitutes containing potassium should also be used with caution.

Nonsteroidal anti-inflammatory drugs. There is some evidence to suggest that concomitant administration of NSAIDs such as indomethacin may reduce the response to ACE inhibitors, but further data are needed to clarify whether such an effect is of clinical significance. Further, concomitant administration of the two classes of agents may increase the risk of hyperkalaemia.

Agents having vasodilator activity. Data on the effect of concomitant use of other vasodilators in patients receiving captopril for heart failure are not available. Therefore, glyceryl trinitrate 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 therapy, such agents should be administered cautiously and perhaps at lower dosage.

Haemodialysis membranes. Hypersensitivity-like (anaphylactoid) reactions have been reported with high flux dialysis membranes (See PRECAUTIONS).

Alpha blocking agents. Concomitant use of alpha blocking agents may increase the antihypertensive effects of captopril and increase the risk of orthostatic hypotension.

Mammalian Target of Rapamycin (mTOR) Inhibitors. Patients taking concomitant mTOR inhibitor (e.g., temsirolimus, sirolimus, everolimus) therapy may be at increased risk for angioedema.

Co-trimoxazole (trimethoprim/sulfamethoxazole). Patients taking concomitant co-trimoxazole (trimethoprim/sulfamethoxazole) may be at increased risk for hyperkalaemia (See PRECAUTIONS).

Laboratory tests
Captopril may cause a false positive urine test for acetone.

ADVERSE EFFECTS

Reported incidences are based on clinical trials involving approximately 7,000 patients treated with captopril.

More Common Reactions
Cardiovascular. Hypotension occurs in about 2% of patients (See PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Dermatological. Rash occurred in 3.8% of patients with normal renal function and 13.1% of patients with evidence of prior renal function impairment. The rash is usually pruritic and maculopapular, but rarely urticarial, and generally occurs during the first four weeks of treatment. It is usually self-limited and reversible and may respond to antihistamine therapy.

In the majority of patients, the condition resolves with the continuation of therapy.

The rash was sometimes accompanied by fever and arthralgia, and in 7 to 10% of patients, by eosinophilia and/or positive antinuclear antibody (ANA) titres.

Cough. Cough has been reported in 0.5 to 2% of patients in clinical trials of captopril (See PRECAUTIONS).

Taste disturbances (dysgeusia). 1.6% of patients receiving 150 mg or less of captopril per day developed a diminution or loss of taste perception. At doses in excess of 150 mg/day, 7.3% of patients experienced this effect. Taste impairment is reversible and usually self-limited to two to three months, even with continued drug administration. Weight loss may be associated with the loss of taste.

Less Common Reactions
Cardiovascular. Tachycardia, chest pain and palpitations have been observed in about 1% of patients.

Angina pectoris, myocardial infarction, Raynaud's phenomenon and congestive heart failure have occurred in 0.2 to 0.3% of patients. Cardiac arrest, cerebrovascular accident/insufficiency, rhythm disturbances/orthostatic hypotension, syncope.

Gastrointestinal. Gastric irritation, abdominal pain and pancreatitis have been reported. Nausea, vomiting, diarrhoea, anorexia and constipation may occur. Stomatitis resembling aphthous ulcers, tongue ulceration and a scalded sensation of the oral mucosa have been reported.

Cases of hepatitis have been reported in association with captopril administration. The predominant form of captopril associated hepatic injury is cholestasis, although mixed or pure hepatocellular injury has also been reported.

Genitourinary. Proteinuria (See PRECAUTIONS). Renal insufficiency, acute renal failure, polyuria, oliguria and urinary frequency have been reported in 0.1 to 0.2% of patients. Cases of nephrotic syndrome and glomerulopathy have also been reported.

Haematological and reticuloendothelial. Neutropenia/agranulocytosis (See PRECAUTIONS). Reversible lymphadenopathy, eosinophilia, anaemia, pancytopenia and thrombocytopenia have been reported.

Dermatological. Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been observed in approximately 1 in 1000 patients (See PRECAUTIONS). Flushing or pallor has been reported in 0.2 to 0.5% of

patients. Bullous pemphigus, erythema multiforme (including Stevens Johnson syndrome), exfoliative dermatitis, photosensitivity.

Other. Paraesthesiae of the hands, serum sickness-like syndrome, myalgia, fatigue, malaise and dizziness have been reported. Dry mouth, dyspnoea, bronchospasm, disturbed vision, itching and/or dry eyes, impotence, loss of libido and insomnia have occurred rarely, often in patients on multiple drug therapy. Asthenia and gynaecomastia.

Severe or life-threatening reactions
Angioedema/hypotension (See PRECAUTIONS).
Neutropenia/agranulocytosis (See PRECAUTIONS).

Altered laboratory findings
Elevations of hepatic transaminases, alkaline phosphatase and serum bilirubin have occurred but no causal relationship to captopril use has been established.

A transient elevation BUN and serum creatinine may occur, especially in patients who are volume depleted or who 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 (See PRECAUTIONS). Hyponatraemia may occur, particularly in patients receiving a low sodium diet or concomitant diuretics.

Changes in blood cell counts and anaemia have occurred during treatment with captopril (See ADVERSE EFFECTS, Uncommon reactions, Haematological and reticuloendothelial).

Post-Introduction Safety Experience
Other clinical adverse effects reported since the medicine was marketed are listed below by body system. In this setting, an incidence or causal relationship cannot be accurately determined.

Foetal/Neonatal Morbidity and Mortality. The use of ACE inhibitors during 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 resulting from decreased foetal renal function; oligohydramnios in this setting has been associated with foetal limb contractures, craniofacial deformation and hypoplastic lung development. Prematurity, intrauterine growth retardation and patent ductus arteriosus have also been reported. More recently, prematurity, patent ductus arteriosus and other structural cardiac malformations, as well as neurologic malformations, have been reported following exposure limited to the first trimester of pregnancy (See Precautions – Use in Pregnancy).

Musculoskeletal. Myasthenia.

Nervous/Psychiatric. Ataxia, confusion, depression, nervousness, somnolence, insomnia, dream abnormality, hallucinations.

Respiratory. Eosinophilic pneumonitis, rhinitis.

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.

DOSAGE AND ADMINISTRATION

Administration

A first dose of hypotensive effect, severe in some patients, may occur. To minimise this effect, the dosage should be individualised and titrated from a low starting dose to the maintenance dose.

Captopril Sandoz should be taken one hour before meals.

Dosage

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 regime for one week before starting Captopril Sandoz.

In most patients, a starting dose of 12.5 mg may be used. The dose may then be increased to 25 mg twice daily. If a satisfactory reduction of blood pressure has not been achieved after two to four weeks, the dose of Captopril Sandoz may be increased to 50 mg twice daily.

Concomitant sodium restriction may be beneficial when Captopril Sandoz is used alone.

In patients in whom a satisfactory reduction in blood pressure is not achieved after a further two weeks at this dosage, it is likely that the hypertension may have a substantial volume dependent component. In these patients it may be appropriate to add a thiazide diuretic. The diuretic dose may be increased at one to two week intervals until its highest usual antihypertensive dose is reached. The usual effective dose of Captopril Sandoz in mild to moderate hypertension does not exceed 50 mg twice daily.

In patients with severe refractory hypertension, or on high diuretics, low salt diet or dialysis, a lower starting dose (6.25 to 12.5 mg) may be used, with titration to daily doses of 25 or 50 mg twice daily.

If Captopril Sandoz is being started in a patient already receiving a diuretic. Captopril Sandoz therapy should be initiated under close medical supervision (See PRECAUTIONS, INTERACTIONS WITH OTHER MEDICINES).

In severe hypertension where further blood pressure reduction is required, larger or more frequent dosing may be necessary. A daily dose of Captopril Sandoz 75 mg twice daily should not normally be exceeded.

For patients with accelerated or malignant hypertension, particularly those unresponsive to convention therapy, it may be necessary to implement the schedule given above at intervals of 24 hours, under continuous medical supervision until a satisfactory blood pressure response is obtained or the maximum dose of Captopril Sandoz is reached.

Myocardial infarction. Therapy may be initiated as early as three days following a myocardial infarction. After an initial dose of 6.25 mg, Captopril Sandoz therapy should be increased as tolerated to 25 mg three times daily during the next several days and to a final target dose of 50 mg three times daily over the next several weeks.

If symptomatic hypotension occurs, a dosage reduction may be required. Subsequent attempts at achieving the target dose of 150 mg should be based on the patient's tolerance to Captopril Sandoz.

Captopril Sandoz may be used in patients treated with other postmyocardial infarction therapies, e.g. thrombolytics, aspirin and ß-blockers.

Heart failure. Captopril Sandoz therapy must be started under close medical supervision. It should be added to convention treatment with a diuretic (and digitalis where indicated).

Patients with cardiac failure may demonstrate sensitivity to the effects of Captopril Sandoz in the early stages of therapy.

In patients in whom greater sensitivity may be suspected (e.g. sodium depletion and/or high doses of diuretics), the hypotensive effects of the first dose may be minimised by the use of a 2.5 mg starting dose. This product should not be used to initiate therapy in such patients as the smallest achievable dose with Captopril Sandoz Tablets is 6.25 mg. In other patients, a starting dose of 6.25 mg three times daily may be used, although a transient hypotensive effect may occur at this dosage.

The maintenance dose of Captopril Sandoz is usually in the range 25 to 75 mg twice daily. Where possible, a period of at least two weeks should be allowed before dose increase within this range. A maximum daily dose of 150 mg should normally not be exceeded.

Patients treated for severe congestive heart failure should be cautioned to increase their physical activity slowly.

Diabetic nephropathy. In patients with diabetic nephropathy, the recommended dose of captopril is 75 to 100 mg daily, in divided doses.

Clinical trials in normotensive type 1 diabetic patients with microalbuminuria (albumin excretion rate between 30 and 300 mg/day) showed that captopril at a dose of 50 mg twice daily attenuated the progression of the disease.

Clinical trials in normotensive and controlled hypertensive type 1 diabetic patients with overt proteinuria (total protein excretion > 500 mg/day) demonstrated that captopril at a dose of 25 mg three times daily had significant beneficial effects by reducing the need for dialysis and transplantation or the occurrence of death.

The effects of captopril were independent of, and additional to, its antihypertensive activity. If further blood pressure reduction is required, other antihypertensive agents such as diuretics, beta-adrenoreceptor blockers, centrally acting agents or vasodilators may be used in conjunction with captopril.

Impaired renal function. Captopril excretion is reduced in the presence of impaired renal function. Accordingly, for patients with significant renal impairment, initial daily dosage of Captopril Sandoz should be reduced, and smaller increments utilised for titration which should be quite slow (one to two week intervals). After the desired therapeutic effect has been achieved, the total daily dose should be reduced or the dose intervals increased. Captopril is removed by haemodialysis.

When concomitant diuretic therapy is required, a loop diuretic (e.g. frusemide) rather than a thiazide diuretic is preferred in patients with impaired renal function.

OVERDOSAGE

Contact the Poisons Information Centre on telephone 13 11 26 for advice on management of overdose.

Treatment
Treatment should be symptomatic if overdosage occurs.

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 haemodialysis, there are inadequate data concerning the effectiveness of haemodialysis 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.

PRESENTATION AND STORAGE CONDITIONS

Tablets

12.5mg - Round tablets with a "snap tab" break mark on one side, convex on the other side, uniform white surface – diameter 6.0-6.2mm.
HDPE Bottle of 90 tablets.*
Blisters of 90 tablets.

25mg - Round tablets of a "cloverleaf" shape with facet and a crossed breakmark on both sides, uniform white surface – diameter 8.0-8.2mm.
HDPE Bottle of 90 tablets.*
Blisters of 90 tablets.

50mg - Round tablets of a "cloverleaf" shape with facet and a crossed breakmark on both sides, uniform white surface – diameter 10.0-10.2mm.
HDPE Bottle of 90 tablets.*
Blisters of 90 tablets.

All pack sizes may not be marketed.

Store below 25ºC.
Protect from moisture.

NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty Ltd
ABN 60 075 449 553
54 Waterloo Road
Macquarie Park, NSW 2113
Australia
Tel: 1800 726 369

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 30/06/1997

DATE OF MOST RECENT AMENDMENT: 03/08/2017