Presentation
APO-CAPTOPRIL 12.5mg tablets are white, flat-faced, capsule shaped, 3.3mm x 6.4mm, partially scored on both sides and identified APO on one side with 12.5 on the other. Each tablet contains 12.5mg of captopril and typically weighs 47.5mg.

APO-CAPTOPRIL 25mg tablets are white, biconvex, square, 6.4mm, quadriscored on one side and identified APO over 25 on the other. Each tablet contains 25mg of captopril and typically weighs 95mg.

APO-CAPTOPRIL 50mg tablets are white, biconvex, oval capsule shaped, 11.3mm x 5.8mm, partially scored and identified APO-50 on one side. Each tablet contains 50mg of captopril and typically weighs 190mg.

APO-CAPTOPRIL 100mg tablets are white, oval biconvex tablets, 14.6 x 7.4mm with a partial bisect and engraved APO-100 on one side. Each tablet contains 100mg captopril and typically weighs 380mg.

Indications
Hypertension
Captopril is indicated for the treatment of hypertension in adult and paediatric 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.

Heart Failure
Captopril is indicated in clinically stable patients with heart failure. In such patients it is recommended that Captopril be administered with a diuretic

Myocardial Infarction
Captopril is indicated in clinically stable patients with asymptomatic and symptomatic left ventricular dysfunction following myocardial infarction to improve survival and reduce the risk of recurrent myocardial infarction or hospitalisation for heart failure.

Diabetic Nephropathy
Captopril is indicated for the treatment of diabetic nephropathy in Type 1 diabetes with or without hypertension. In these patients captopril prevents the progression of renal disease and reduces associated clinical sequelae (dialyses, renal transplantation and death).

Dosage and Administration
Dosages must be individualised, and medication is maximally absorbed if taken one hour before meals. Refer to Warnings and precautions regarding hypotension in salt and volume depleted patients.

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 50 mg once daily or 25 mg twice daily. If a satisfactory reduction of blood pressure has not been achieved the dose of captopril may be increased and the total dosage should then be given in divided doses. Alternatively, a small dose of thiazide diuretic may be added prior to increasing the dose of captopril. The usual maintenance dose is 50 to 100 mg daily. For patients already receiving a diuretic, the initial dose of captopril should be administered with care (refer to Warnings and precautions).

The usual effective dose of captopril in mild to moderate hypertension does not exceed 100 mg per day. However, in severe hypertension where further blood pressure reduction is required, the dose may be increased incrementally (while continuing the diuretic) and a three times a day dosage schedule may be considered. A maximum daily dose of 450 mg captopril should not be exceeded. For patients with severe hypertension who are on multiple antihypertensive therapy it may be impractical to discontinue all therapy prior to starting captopril. In such patients captopril would usually be used in combination with a thiazide diuretic, therefore, the diuretic should be continued and other currently administered antihypertensive agents should be discontinued according to the instructions of the manufacturer. Captopril 25 mg twice a day or three times a day should be initiated under close medical supervision.

For patients with accelerated or malignant hypertension, particularly those unresponsive to conventional therapy, the dosage may be increased at 24 hour intervals or less under continuous medical supervision, until a satisfactory blood pressure response is obtained or the maximum dose of captopril is reached. In this regimen, addition of a more potent diuretic, eg, furosemide may also be indicated. When captopril is used alone, concomitant sodium restriction may be beneficial. Captopril may be used advantageously in conjunction with other antihypertensive agents.

Heart failure
Captopril therapy must be started under close medical supervision. It should be added to conventional treatment with diuretic (and digitalis where indicated). Initiation of therapy requires consideration of recent diuretic therapy and the possibility of severe salt/volume depletion. In patients with either normal or low blood pressure, who have been vigorously treated with diuretics and who may be hyponatremic and/or hypovolemic a starting dose of 6.25 or 12.5 mg twice daily may minimise the duration of any transient hypotensive effect (refer to Warnings and precautions - Hypotension); for these patients, titration to the usual daily dosage can then occur within the next several days. For most patients the usual initial daily dose is 25 mg twice daily. The usual maintenance dose is 25 to 50 mg twice daily. After a dose of 50 mg three times daily is reached, further increases in dosage should not normally be given. The usual maximum daily dose is 150 mg but this may be increased at the discretion of the physician.

Post-Myocardial Infarction
The recommended dose for long-term prophylactic use in patients who have survived a myocardial infarction is a target dose of 150 mg daily. Therapy may be initiated as early as 3 days following a myocardial infarction. The initial recommended dosage is captopril 6.25 or 12.5 mg. If the dose is well tolerated, captopril may be increased to 37.5 mg daily then 75 mg daily in divided doses during the next several days and then over the next several weeks to a recommended daily dose of 150 mg daily given twice daily or three times daily.

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.

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

Diabetic Nephropathy
In patients with diabetic nephropathy, the recommended daily dose of captopril is 75 to 100 mg in divided doses. If further blood pressure reduction is required, other antihypertensive agents such
as diuretics, beta-adrenoceptor blockers, centrally acting agents or vasodilators may be used in conjunction with captopril.

**Dosage adjustment in renal impairment**

Captopril in divided doses of 75 to 100 mg/day was well tolerated in patients with diabetic nephropathy and mild to moderate renal impairment. (refer to Warnings and Precautions - Hyperkalaemia). Because captopril is excreted primarily by the kidneys, excretion rates are reduced in patients with impaired renal function. These patients will take longer to reach steady-state captopril levels and will reach higher levels for a given daily dose than patients with normal renal function. Therefore, these patients may respond to smaller or less frequent doses. Accordingly, for patients with significant renal impairment, initial daily dosage of captopril should be reduced. Smaller increments used for titration, which should be should be quite slow (one-to two-week intervals). After the desired therapeutic effect has been achieved, the dose should be slowly back-titrated to determine the minimal effective dose. When concomitant diuretic therapy is required, a loop diuretic (e.g., furosemide), rather than a thiazide diuretic, is preferred in patients with severe renal impairment.

**Children**

The initial dose of captopril of 0.3 mg/kg administered under close medical supervision. Infants and older children more likely to develop hypotension, such as those on diuretic therapy may be started on 0.15 mg/kg. Generally the dose of captopril is administered 3 times a day. However, the frequency of dosing must be individualised according to the response of each patient. If a satisfactory reduction of blood pressure has not been achieved, each single dose may be increased at weekly intervals to 0.6, 1.2 and 2.0 mg/kg. For those patients not receiving a diuretic, concomitant diuretic therapy may be instituted. For patients with accelerated hypertension, dosage may be increased at 24 hour intervals or less. A maximum total daily dose of 6.0 mg/kg should not be exceeded. Dosage in infants and patients with renal dysfunction should be reduced appropriately (refer to Warnings and Precautions).

**Contraindications**

Known hypersensitivity to captopril or to any of the inactive ingredients listed in Further Information.

History of angioneurotic oedema relating to previous treatment with an ACE inhibitor. Hereditary or idiopathic angioedema.

Not for use in pregnancy. Embryopathy can occur in second or third trimester. All ACE inhibitors, including captopril are contraindicated in pregnancy because of the potential risk of foetotoxicity.

**Warnings and Precautions**

**Anaphylactoid and possibly related reactions**

Possibly 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, 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. The aetiology is thought to be non-immunogenic and may be related to accentuated bradykinin activity. Usually the angioedema involves non-pitting 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. Where 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 where it was not. Because of the potential severity of this rare event another ACE inhibitor should not be used in patients with history of angioedema to a drug of this class.

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.

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 where 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 aphaeresis membrane exposure

Patients haemodialysed with 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 polysulphone PSF for haemodialysis).

Proteinuria

Total urinary proteins greater than 1 g per 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 150 mg per day), or both. In mild to moderate hypersensitive patients the incidence dropped to 0.06%. Alterations in renal function (as assessed by blood urea nitrogen and serum creatinine) were infrequent in these patients and did not occur in those who had no prior renal disease. In patients without prior evidence of renal disease the incidence of proteinuria was 0.5.
percent. In those patients without prior evidence of renal disease and receiving 150 mg of captopril or less per day the incidence was 0.2 percent.

Nephrotic syndrome (hypoalbuminaemia, oedema and protein excretion greater than 3 grams per day) occurred in about one-fifth of the proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. Parameters of renal function such as BUN and creatinine were seldom altered in the patients proteinuria.

In a multicentre, double-blind, placebo-controlled trial in 207 patients with diabetic nephropathy and proteinuria 500 mg per day or above receiving captopril 75 mg/day for a median of 3 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.

For patients with prior renal disease or those receiving captopril at doses greater than 150 mg per day, urinary protein estimations (dipstick) should be done prior to treatment and periodically thereafter. If these show increasing amounts of urinary protein, a 24 hour quantitative determination of urinary protein should be done. If this exceeds on gram per day, the benefits and risks of continuing captopril should be evaluated.

**Neutropenia/agranulocytosis**

Neutropenia has occurred in some patients receiving captopril, but the risk of neutropenia is dependent on the clinical status of the patients especially 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 impairment (serum creatinine at least 1.6 mg/dl) but no collagen vascular disease or coadministered immunosuppressant agents, neutropenia occurred in 0.3 percent of cases. Daily doses of captopril were relatively high in these patients, particularly in view of their diminished renal function. 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 (and then with caution) since neutropenia has occurred in 8 out of the 124 such patients in clinical trials. Similar caution should be exercised in patients receiving immunosuppressant agents.

Neutropenia was noted 2 to 13 weeks after captopril treatment commenced 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. Bone marrow examination in patients with neutropenia consistently showed myeloid hypoplasia, frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes. Neutropenia was associated with significant alteration of peripheral red blood cell or platelet counts in 6 patients.

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% 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 cell count
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was not progressive and the effect was no longer apparent after 12 weeks in most patients. The significance of these changes is uncertain.

In clinical trials, neutrophil counts returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13 percent of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or on immunosuppressant therapy, or a combination of these complicating factors.

For patients with significantly impaired renal function, collagen vascular disease, or who are receiving immunosuppressant agents and for patients with pre-existing neutropenia, white blood cell and differential counts should be performed prior to therapy and at regular intervals thereafter. Evaluation of the hypertensive or heart failure patient should include assessment of renal function.

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.

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 per cubic millimeter), 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.

Although most patients tolerate the antihypertensive effects of captopril well, those already on diuretic therapy may occasionally experience dizziness or light-headedness, usually mild, indicative of hypotension that may occur within one hour of the first dose. In most instances, symptoms are relieved simply by instructing the patients to lie down. In patients who are salt/volume depleted (such as those receiving aggressive diuretic therapy), particularly those with either severe, renin dependent hypertension (eg. renovascular hypertension) or severe congestive heart failure, exaggerated hypotensive responses have occurred, again usually within one hour of the initial dose of captopril. The possibility of this occurrence can be lessened in these patients by discontinuing diuretic therapy or by significantly reducing the diuretic dose for 4 to 7 days prior to initiating captopril. By commencing captopril therapy with small doses, (6.25 or 12.5 mg), the duration of any hypotensive effect is reduced. The likelihood of an exaggerated hypotensive effect is reduced. The likelihood of an exaggerated hypotensive response can be predicted early if the patient is under medical supervision during the first hour after initial dosing; and if necessary, it can be rapidly reversed by intravenous infusion of normal saline. A hypotensive episode following the initial dose of captopril dose not preclude further doses which can be given without difficulty once the blood pressure has increased.

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

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 medical supervision. Such patients should be followed closely for the first 2 weeks of treatment and whenever the dose is increased, or diuretic therapy is commenced or increased. Patients treated for severe congestive heart failure should be cautioned to increase their physical activity slowly.

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 difficulty 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.

**Impaired renal function**

**Hypertension**

Some patients with renal disease, particularly those with bilateral renal artery stenosis, have developed increases in BUN and serum creatinine after reduction of blood pressure with captopril, usually in conjunction with a diuretic. Captopril dosage reduction or discontinuation of diuretic, or both 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. 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**

Some patients with heart failure have experienced a reduction in renal function during long-term treatment that usually stabilised at the reduced level. Less than 5% of patients, generally those with 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.
Hyperkalaemia
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including captopril. 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; 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 (e.g., heparin). Diabetic patients, and elderly diabetic 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 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 as part of the differential diagnosis of cough.

Hepatic failure
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic neurosis 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 ACE inhibitors and receive appropriate medical attention.

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. If hypotension occurs and is considered to be due to this mechanism it can be corrected by volume expansion.

Aortic stenosis
Captopril, as with any agent that reduces vascular resistance, should be used only with extreme caution in patients with aortic stenosis because of the potentially harmful consequences of reduced coronary perfusion secondary to the reduced blood pressure. Patients treated for severe congestive heart failure should be cautioned to increase their physical activity slowly.
Paediatric use
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. There is limited experience reported in the literature with the use of captopril in the paediatric population; dosage, on a weight basis, was generally reported to be comparable to or less than that used in adults. Infants, especially newborns, may be more susceptible to the adverse 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 captopril doses should be used with the patient under close medical supervision. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

Pancreatitis
May cause pancreatitis. Pancreatitis may occur with ACE inhibitors and patients with abdominal pain on ACE inhibitors should be tested accordingly.

Lactose intolerance
Since this medicinal product contains lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Pregnancy and lactation
Use in pregnancy
Category D
This category includes medicines 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.

There is a potential risk of foetal hypotension, decreased birth weight and decreased renal perfusion or anuria in the foetus from in utero exposure to ACE inhibitors. When taken during the second and third trimesters, ACE inhibitors cause a range of abnormalities including renal dysfunction and oligohydramnios. These can be associated with foetal death in utero. Use of ACE inhibitors during this period has been associated with foetal and neonatal injury including hypotension, renal failure, hyperkalaemia, and/or skull hypoplasia in the newborn. Maternal oligohydramnios, presumably representing decreased foetal renal function, has occurred and may result in limb contractures, craniofacial deformations, hypoplastic lung development and intra-uterine growth retardation. Prematurity and patent ductus arteriosus have also been reported.

Although no adverse foetal effects have been linked to first trimester drug use of ACE inhibitors, the number of exposures reported is too small to determine conclusively that ACE inhibitors are safe in the first trimester. 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 the first 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.

Pregnant women who are taking ACE inhibitors should be changed as quickly as possible to other antihypertensive medication to maintain normal blood pressure. It is generally advisable not...
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to use ACE inhibitors for the management of hypertension in women who are likely to become pregnant.

Use in lactation
Residual captopril may be present in breast milk at levels corresponding to 0.014% of the maternal dose. Captopril is considered safe in breastfeeding.

Effects on ability to drive and use machines
This medicine is likely to produce minor or moderate adverse effects. Individual responses to medication may vary. Certain adverse effects that have been reported with captopril may affect some patient's ability to drive or operate machinery (refer to Adverse effects).

Other
Preclinical safety data
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.

Adverse Effects
Clinical trial data
Reported incidences are based on clinical trials involving approximately 7,000 patients treated with captopril.

Skin
A rash occurred in 8.5 percent of patients with normal renal function and 13 percent of patients with evidence of prior renal function impairment. It was dose related, having occurred only in 7 percent of patients at dose of 150 mg or less per day. The rash is usually pruritic and maculopapular, but rarely urticarial and generally occurs during the first 4 weeks of treatment. It usually is self-limiting and reversible and may respond to antihistamine therapy. The rash is usually mild and disappears within a few dosage reduction, short-term treatment with an antihistamine and/or discontinuing 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. Pruritus, flushing, fever, arthralgia, eosinophilia, a reversible pemphigoid-like lesion and photosensitivity have also been reported.

Gastrointestinal
Two percent of patients receiving 150 mg or less per day of captopril developed a diminution or loss of taste perception. At doses in excess of 150 mg per day, 7 percent of patients experienced this effect. Taste impairment is reversible and usually self-limiting (2 to 3 months). In most patients the condition resolved with the continuation of therapy. Weight loss may be associated with the loss of taste.

Hepatic
Elevation of liver enzymes have been noted in a few patients receiving the medication although no causal relationship has been found.

Renal
Proteinuria (refer to Warnings and Precautions).
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Transient elevations of BUN and creatinine (refer to Warnings and precautions). Increase in the serum potassium concentrations and acidosis (refer to Warnings and precautions). Renal insufficiency, renal failure, nephrotic syndrome, polyuria, oliguria and urinary frequency.

Haematologic
Neutropenia/agranulocytosis, Reversible lymphadenopathy, anaemia, thrombocytopenia and pancytopenia (refer to Warnings and Precautions).

Cardiovascular
Hypotension occurs in about 2% of patients. Hypotension may occur after initiation of captopril therapy in patients with heart failure, renin-dependent hypertension or who are significantly volume-depleted (refer to Warnings and precautions). Tachycardia, chest pain and palpitations have each been observed in approximately 1% of patients. Angina pectoris, myocardial infarction, Raynaud's phenomenon and congestive heart failure have occurred in 0.2 to 0.3% or less of patients.

Immunologic
Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been reported in approximately 0.1% of patients. Angioedema involving the upper airways has caused fatal airways obstruction.

Respiratory
Cough has been reported in 0.5 to 2% of patients treated with captopril in clinical trials.

Less common events
The following have been reported in about 0.5 to 2 percent of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials: gastric irritation, abdominal pain, nausea, vomiting, diarrhoea, anorexia, constipation, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnoea, alopecia, paraesthesiae of the hands, serum sickness-like syndrome, itching and/or dry eyes.

Stomatitis resembling aphthous ulcers, tongue ulceration and a scalded sensation of the oral mucosa have been reported.

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.

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.

Post-marketing surveillance data
Other clinical adverse effects reported since the drug was marketed are listed below by body system. In this setting, an incidence or causal relationship cannot be accurately determined.

General: asthenia, gynaecomastia.

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

Please refer to Medsafe website (www.medsafe.govt.nz) for the most recent datasheet
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Dermatologic: bullous pemphigus, erythema multiforme (including Stevens-Johnson syndrome), exfoliative dermatitis.

Gastrointestinal: pancreatitis, glossitis, dyspepsia.

Hematologic: anaemia, including aplastic and haemolytic.

Hepatobiliary: jaundice, hepatitis, including rare cases of hepatic necrosis, cholestasis - the predominant form of captopril associated hepatic injury is cholestasis, although mixed or pure hepatocellular injury has also been reported.

Metabolic: symptomatic hyponatremia.

Musculoskeletal: myalgia, myasthenia.

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

Respiratory: bronchospasm, eosinophilic pneumonitis, rhinitis.

Special Senses: blurred vision.

Urogenital: impotence.

As with other ACE inhibitors, a syndrome has been reported which may include: fever, myalgia, arthralgia, interstitial nephritis, vasculitis, rash or other dermatologic manifestations, eosinophilia and an elevated ESR.

Foetal/neonatal morbidity and mortality
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 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 (refer to Warnings and precautions).

Altered laboratory findings
Serum electrolytes
Small increases in the serum potassium concentration frequently occur, especially in patients with renal impairment. Hyponatremia may occur, particularly in patients receiving a low sodium diet or concomitant diuretics.

BUN/serum creatinine
Transient elevations of BUN or serum creatinine may occur, especially in volume or salt depleted patients or those 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.

Please refer to Medsafe website (www.medsafe.govt.nz) for the most recent datasheet
Haematologic
A positive ANA has been reported. Changes in blood cell counts and anaemia have occurred during treatment with captopril.

Liver function tests
Elevations of liver transaminases, alkaline phosphatase, and serum bilirubin have occurred but no causal relationship to captopril use has been established.

Interactions

Medicines and other pharmacologically active substances

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 and especially those in whom diuretic therapy was recently instituted, or in those with intravascular volume depletion, may occasionally 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.

Agents having vasodilator activity
Data on the effect of concomitant use of other vasodilators in patients receiving captopril for heart failure are not available. Accordingly, glyceryl trinitrate or other nitrates (as used for management of angina) or other agents having vasodilator activity should, if possible, be discontinued before commencing captopril treatment. If resumed during captopril therapy, such agents should be administered cautiously, and perhaps at a lower dosage.

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

Agents affecting sympathetic activity
The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Therefore, agents affecting sympathetic activity (eg. ganglionic blocking agents or adrenergic neuron blocking agents) should be used with caution. Beta-adrenergic blocking agents 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 decrease 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 hypokalaemia, and then with caution, since they may lead to a significant increase in serum potassium. Salt substitutes containing potassium should also be used with caution.

Please refer to Medsafe website (www.medsafe.govt.nz) for the most recent datasheet
Inhibitors of endogenous prostaglandin synthesis
There is some evidence to suggest that concomitant administration of indomethacin may reduce the response to ACE inhibitors, especially in cases of low renin hypertension but further data are needed to clarify whether such an effect is of clinical significance. Other non-steroidal anti-inflammatory agents may also have this effect. Furthermore, concomitant administration of the two classes of agents may increase the risk of hyperkalaemia.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics
Concomitant use of renin-angiotensin system inhibiting drug (ACE inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID, including COX-2 inhibitor) and a thiazide diuretic may increase the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combinations of these agents should be administered with caution, especially in the elderly and in patients with pre-existing renal impairment. Renal function (serum creatinine) should be monitored after initiation of concomitant therapy, and periodically thereafter.

Lithium
Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. These agents 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.

Abnormal laboratory test results
Captopril may cause a false-positive urine test of acetone.

Overdosage
Signs and symptoms
Correction of hypotension would be of primary concern.

Management
Volume expansion with an intravenous infusion of normal saline is the treatment of choice for normalisation of the 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.

Further Information

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

Pharmacotherapeutic group
C09AA01 - ACE inhibitors, plain, captopril.
Apo-Captopril

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

Mechanism of action
Captopril contains captopril, an inhibitor of angiotensin converting enzyme (ACE), a peptidyldepeptide carboxyhydrolase, which converts angiotensin I to angiotensin II, a potent endogenous vasoconstrictor substance. The mechanism of action of captopril has not yet been fully elucidated, however its beneficial effect in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. However, there is no consistent correlation between renin levels and response to the medicine. 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 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 and this is reflected by a decrease in the pressor substance, angiotensin II, and 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. The reduction of angiotensin II leads to decreased aldosterone secretion, and as a result, small increases in serum potassium may occur along with sodium and fluid loss. 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.

Reductions in blood pressure are usually maximal 60 to 90 minutes after oral administration. The blood pressure lowering effects of captopril and thiazide-type diuretics are additive. Abrupt withdrawal of captopril has not been associated with rapid increase in blood pressure.

In patients with heart failure, significantly decreased systemic vascular resistance and blood pressure (afterload), reduced pulmonary capillary wedge pressure (preload) and pulmonary vascular resistance, increased cardiac output and increased exercise tolerance time have been demonstrated. These haemodynamic and clinical effects occur after the first dose and appear to persist for the duration of therapy.

Following myocardial infarction the loss of functioning myocardium results in hypertrophy of the residual myocardium and dilatation of the ventricle (remodelling). In the long term this may lead to the onset of clinically evident cardiac failure. 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 o 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 i.e. coronary artery bypass graft surgery and percutaneous transluminal coronary angioplasty (risk reduction 24%, p=0.014).

Potential mechanisms 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
Apo-Captopril
Captopril 12.5mg, 25mg, 50mg and 100mg tablet USP

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-treatment 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<0.01), and a 51% risk reduction for the combined morbidity/mortality endpoint of end-stage renal disease (dialysis or renal transplantation) or death (p<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 patients with diabetes mellitus and microalbuminuria, captopril reduced albumin excretion rate and attenuated the decline in glomerular filtration rate during two years of treatment. 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.

Pharmacodynamic effects
Administration of captopril results in a reduction of peripheral arterial resistance in hypertensive patients with either no change or an increase in cardiac output. 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.

Onset and duration of action
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.

Please refer to Medsafe website (www.medsafe.govt.nz) for the most recent datasheet
Pharmacokinetics

Absorption
Following oral administration of captopril, rapid absorption occurs with peak blood levels of approximately 1 mcg/l being found within 30 minutes to 1 hour after a 100 mg dose. The average minimal absorption is approximately 75%. The presence of food in the gastrointestinal tract reduces absorption by 25% to 40%. 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
Approximately 30% of the circulating drug is bound to plasma proteins. Captopril appears to be distributed between three compartments in humans. The terminal phase volume of distribution (2 litres/kg) suggests that captopril is distributed into deep tissues. Captopril does not cross the blood-brain barrier to any significant extent.

Biotransformation
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 ACE. Captopril and its metabolites (captopril dimer and conjugates with endogenous thiol compounds, e.g. captopril-cysteine) are excreted principally in the urine. In vitro studies suggest that the metabolites are labile and that interconversions may occur in vivo.

Elimination
After administration of a radiolabelled oral dose, the apparent elimination half-life for total radioactivity in blood is about 12 hours for the 12 to 48 hours time interval. The half-life of unchanged captopril is approximately 2 hours. In a 24 hour period, 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.

Special patient considerations
Renal impairment
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. Excretion of captopril is reduced in patients with renal impairment and hence drug accumulation is a possibility.

Please refer to Medsafe website (www.medsafe.govt.nz) for the most recent datasheet
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Other

Chemical Structure

Excipients

Apo-Captopril contains the following excipients: Croscarmellose sodium, hydrated silica, magnesium stearate, microcrystalline cellulose and lactose monohydrate.

This medicine contains lactose.

Pharmaceutical Precautions

Instructions for use/handling
Nil.

Incompatibilities
None known.

Shelf-Life
Bottles 60 months
Blister packs 24 months

Special precautions for storage
Store at or below 25°C. Protect from heat, light and moisture.

Package Quantities
Bottles of 50, 100, 250 and 500 tablets for all strengths.
Blister packs of 30 and 90 tablets for all strengths.

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Apo-Captopril
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Medicine Schedule
Prescription-Only medicine.

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Telephone: (09) 444-2073

Date of Preparation
21 September 2012

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