SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Captopril 12.5 mg Tablets
Captopril 25mg Tablets
Captopril 50mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 12.5 mg of Captopril.
Excipient with known effect: Also contains 12.5mg of lactose.

Each tablet contains 25 mg of Captopril.
Excipient with known effect: Also contains 25mg of lactose.

Each tablet contains 50 mg of Captopril.
Excipient with known effect: Also contains 50mg of lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

For 12.5mg tablets:
White to almost white, round, biconvex, uncoated tablets with "12.5" debossed on one side.

For 25mg tablets:
White to almost white, round, flat, bevelled edged, uncoated tablets with score line on one side and "25" debossed on the other side.

For 50mg tablets:
White to almost white, round, flat, bevelled edged, uncoated tablets with score line on one side and "50" debossed on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hypertension: The management of mild to moderate hypertension. In severe hypertension it should be used where standard therapy is ineffective or inappropriate.

Congestive heart failure: Captopril is indicated for the treatment of congestive heart failure. The drug should be used together with diuretics and, when appropriate, digitalis and beta-blockers. In patients on doses of over 100 mg daily plus or minus a diuretic, in those with severe renal impairment or those with severe congestive heart failure use of captopril should be under specialist supervision.

Myocardial Infarction:

- *Short-term (4 weeks) treatment*: Captopril is indicated in any clinically stable patient within the first 24 hours of an infarction.
- *Long-term prevention of symptomatic heart failure:* Captopril is indicated in clinically stable patients with asymptomatic left ventricular dysfunction (ejection fraction ≤ 40%) following myocardial infarction to improve survival, delay the onset of symptomatic heart failure, reduce hospitalisations for heart failure and reduce recurrent myocardial infarction and coronary revascularisation procedures.

  Before starting therapy, cardiac function should be determined by radionuclide ventriculography or echocardiography.

Type I Diabetic Nephropathy: Captopril is indicated in insulin dependent diabetics for the treatment of macroproteinuric diabetic nephropathy (microalbuminuria greater than 30 mg/day) (See Section 5.1). Captopril may prevent the progression of the renal disease and reduce associated clinical events e.g. dialysis, renal transplantation and death.
Captopril can be used alone or in combination with other antihypertensive agents (see sections 4.3, 4.4, 4.5 and 5.1).

4.2 Posology and Method of Administration

Posology
Dose should be individualised according to patient's profile (see section 4.4) and blood pressure response. The recommended maximum daily dose is 150mg.

Adults:
Hypertension: Treatment with captopril should be at the lowest effective dose which should be titrated according to the needs of the patient.
The recommended starting dose is 25-50 mg daily in two divided doses. The dose may be increased incrementally, with intervals of at least 2 weeks, to 100-150 mg/day in two divided doses as needed to reach target blood pressure. Captopril may be used alone or with other antihypertensive agents, especially thiazide diuretics (see sections 4.3, 4.4, 4.5 and 5.1). A once-daily dosing regimen may be appropriate when concomitant antihypertensive medication such as thiazide diuretics is added.
In patients with a strongly active renin-angiotensin-aldosterone system (hypovolaemia, renovascular hypertension, cardiac decompensation) it is preferable to commence with a single dose of 6.25 mg or 12.5 mg. The inauguration of this treatment should preferably take place under close medical supervision. These doses will then be administered at a rate of two per day. The dosage can be gradually increased to 50mg per day in one or two doses and if necessary to 100mg per day in one or two doses.

Congestive heart failure: Treatment with captopril for congestive heart failure should be initiated under close medical supervision. The usual starting dose is 6.25mg- 12.5mg BID or TID. Titration to the maintenance dose (75-150mg per day) should be carried out based on patient's response, clinical status and tolerability, up to a maximum of 150mg per day in divided doses. The dose should be increased incrementally, with intervals of at least 2 weeks to evaluate patient's response.

Myocardial infarction:

- ***Short-term treatment*:** Captopril treatment should begin in hospital as soon as possible following the appearance of the signs and/or symptoms in patients with stable haemodynamics. A 6.25mg test done should be administered, with a 12.5mg dose being administered 2 hours afterwards and a 25mg dose 12 hours later. From the following day, captopril should be administered in a 100mg/day dose, in two daily administrations, for 4 weeks if warranted by the absence of adverse haemodynamic reactions. At the end of the 4 weeks of treatment, the patient's state should be reassessed before a decision is taken concerning treatment for the post-myocardial infarction stage.
- ***Chronic treatment:*** if captopril treatment has not begun during the first 24 hours of the acute myocardial infarction stage, it is suggested that treatment be instigated between the 3rd and 16th day post-infarction once the necessary treatment conditions have been attained (stable haemodynamics and management of any residual ischaemia). Treatment should be started in hospital under strict surveillance (particularly of blood pressure) until the 75mg dose is reached. The initial dose must be low (see section 4.4), particularly if the patient exhibits normal or low blood pressure at the initiation of therapy. Treatment should be initiated with a dose of 6.25mg followed by 12.5mg 3 times daily for 2 days and then 25mg 3 times daily if warranted by the absence of adverse haemodynamic reactions. The recommended dose for effective cardioprotection during long-term treatment is 75 to 150mg daily in two or three doses. In cases of symptomatic hypotension, as in heart failure, the dosage of diuretics and/or other concomitant vasodilators may be reduced in order to attain the steady state dose of captopril. Where necessary, the dose of captopril should be adjusted in accordance with the patient's clinical reactions. Captopril may be used in combination with other treatments for myocardial infarction such as thrombolytic agents, beta-blockers and acetylsalicylic acid.

Type I Diabetic nephropathy: In patients with type I diabetic nephropathy, the recommended daily dose is 75-100mg in divided doses. Captopril may be used in combination with other antihypertensive agents, i.e. diuretics, beta blockers, centrally acting agents or vasodilators if the reduction in blood pressure is inadequate with captopril alone.

Patients with renal impairment: Since captopril is excreted primarily via the kidneys, dosage should be reduced or the dosage interval should be increased in patients with impaired renal function. 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.

In patients with impaired renal function, the following daily dose may be recommended to avoid accumulation of captopril.

Creatinine clearance (ml/min/1.73m^2)	Daily starting dose (mg)	Daily maximum dose (mg)
>40	25-50	150
21-40	25	100
10-20	12.5	75
<10	6.25	37.5

Elderly: as with other antihypertensive agents, consideration should be given to initiating therapy with a lower starting dose (6.25 mg BID) in elderly patients who may have reduced renal function and other organ dysfunction (see above 'renal impairment' and section 4.4). Dosage should be titrated against the blood pressure response and kept as low as possible to achieve adequate control.

Paediatric population: The efficacy and safety of captopril have not been fully established. The use of captopril in children and adolescents should be initiated under close medical supervision. The initial dose of captopril is about 0.3mg/kg body weight. For patients requiring special precautions (children with renal dysfunction, premature infants, new-borns and infants, because their renal function is not the same with older children and adults) the starting dose should be only 0.15 mg captopril/kg weight. Generally, captopril is administered to children 3 times a day, but dose and interval of dose should be adapted individually according to patient's response.

Method of Administration
For oral use
Captopril tablets may be taken before, during and after meals.

4.3 Contraindications

- Hypersensitivity to captopril, any other ACE inhibitor or to any of the excipients listed in section 6.1.
- History of angioedema associated with previous ACE inhibitor therapy.
- Hereditary/idiopathic angioneurotic oedema.
- Second and third trimester of pregnancy (see section 4.4 and 4.6)
- Lactation (see section 4.6).
- The concomitant use of Captopril, hard with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.5 and 5.1)
- Concomitant use with sacubitril/valsartan therapy. Captopril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see also sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Pregnancy: ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Hypotension: rarely hypotension is observed in uncomplicated hypertensive patients. Symptomatic hypotension is more likely to occur in hypertensive patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea, vomiting or haemodialysis. Volume and/or sodium depletion should be corrected before the administration of an ACE inhibitor and a lower starting dose should be considered.
Patients with heart failure are at higher risk of hypotension and a lower starting dose is recommended when initiating therapy with an ACE inhibitor. 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 pre-treatment levels, without a decrease in therapeutic efficacy, within two months. Caution should be used whenever the dose of captopril or diuretic is increased in patients with heart failure.
As with any antihypertensive agent, excessive blood pressure lowering in patients with ischaemic cardiovascular or cerebrovascular disease may increase the risk of myocardial infarction or stroke. If hypotension develops, the patient should be placed in a supine position. Volume repletion with intravenous normal saline may be required.
Infants, especially new-borns, 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.

Renovascular hypertension: there is an increased risk of hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE inhibitors. Loss of renal function may occur with only mild changes in serum creatinine. In these patients, therapy should be initiated under close medical supervision with low doses, careful titration and monitoring of renal function.

Renal impairment: The incidence of adverse reactions to captopril is principally associated with renal function since the drug is excreted primarily by the kidney. In cases of renal impairment (creatinine clearance ≤ 40ml/min), the initial dosage of captopril must be adjusted according to the patient's creatinine clearance (see section 4.2), and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine are part of normal medical practice for these patients.
The dose should not exceed that necessary for adequate control and should be reduced in patients with impaired renal function.
Evaluation of the patient should include assessment of renal function (monitoring of potassium and creatinine) prior to initiation of therapy and at appropriate intervals thereafter. Patients with renal impairment should not normally be treated with captopril.

Hypersensitivity / Angioedema: angioedema of the extremities, face, lips, mucous membranes, tongue, glottis or larynx may occur in patients treated with ACE inhibitors including Captopril. This may occur anytime during treatment. However, in rare cases, severe angioedema may develop after months or years of long-term treatment with an ACE inhibitor. In such cases, captopril should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. In those instances where swelling has been confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema involving the tongue, glottis or larynx may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, which

may include subcutaneous epinephrine solution 1:1000 (0.3 ml to 0.5 ml) and/or measures to ensure a patent airway, should be administered promptly. Emergency therapy should be instituted. The patient should be hospitalised and observed for at least 12 to 24 hours and should not be discharged until complete resolution of symptoms has occurred.
Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks. Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see section 4.3).
Intestinal angioedema has also 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 facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, 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 (see section 4.8).
Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema. Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of captopril. Treatment with captopril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5).
Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin in a patient already taking an ACE inhibitor.
Serum potassium ACE inhibitors can cause hyperkalemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. However, in patients with impaired renal function and/or in patients taking potassium supplements (including salt substitutes), potassium-sparing diuretics, trimethoprim or cotrimoxazole also known as trimethoprim/sulfamethoxazole and especially aldosterone antagonists or angiotensin receptor blockers, hyperkalemia can occur. Potassium sparing diuretics and angiotensin receptor blockers should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored (see section 4.5)

Insulin Autoimmune Syndrome (IAS):
Cases of Insulin Autoimmune Syndrome (IAS), including severe hypoglycaemic events have been reported during the treatment with Captopril (see section 4.8). If IAS is suspected, Captopril should be discontinued, and appropriate treatment should be initiated.

Cough: cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy.

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

Hyperkalaemia: Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including captopril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, diabetes mellitus, hypoaldosteronism or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin, co-trimoxazole also known as trimethoprim/ sulfamethoxazole). If concomitant use of the above mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended (see section 4.5).

Combination with Lithium: Captopril is not recommended in association with lithium due to the potentiation of lithium toxicity (see 4.5).

Aortic and mitral valve stenosis/Obstructive hypertropic cardiomyopathy: ACE inhibitors should be used with caution in patients with left ventricular valvular and outflow tract obstruction. As limited experience has been obtained in the treatment of acute hypertensive crises, the use of captopril should be avoided in cases of cardiogenic shock and haemodynamically significant obstruction.

Neutropenia/Agranulocytosis: Neutropenia/Agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors, including captopril. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Captopril should be used with extreme caution in patients with pre-existing impaired renal function, collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors. Some of these patients developed serious infections which in a few instances did not respond to intensive antibiotic therapy.

If captopril is used in such patients, it is advised that white blood cell count and differential counts should be performed prior to therapy, every 2 weeks during the first 3 months of captopril therapy, and periodically thereafter. During treatment all patients should be instructed to report any sign of infection (eg. Sore throat, fever) when a differential white blood cell count should be performed. Captopril and other concomitant medication (see section 4.5) should be withdrawn if neutropenia (neutrophils less than $1000/mm^3$) is detected or suspected.

In most patients neutrophil counts rapidly return to normal upon discontinuing captopril

Proteinuria: Proteinuria may occur particularly in patients with existing renal function impairment or on relatively high doses of ACE inhibitors.

Total urinary proteins greater than 1g per day were seen in about 0.7% of patients receiving captopril. The majority of patients had evidence of prior renal disease or had received relatively high doses of captopril (in excess of 150 mg/day), or both. Nephrotic syndrome occurred in about one-fifth of 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 with proteinuria.

In patients with evidence of prior renal disease should have urinary protein estimations (dip-stick on first morning urine) prior to treatment, and periodically thereafter.
Although membranous glomerulopathy was found in biopsies taken from some proteinuric patients, a causal relationship to captopril has not been established.

Anaphylactoid reactions during desensitisation: There have been rare reports of sustained life-threatening anaphylactoid reactions have been rarely reported in patients undergoing desensitisation treatment with hymenoptera venom while receiving another ACE inhibitor. 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 inhibitor undergoing such desensitisation procedures.

Anaphylactoid reactions during high-flux dialyses/lipoprotein apheresis membrane exposure: Recent clinical observations have shown a high incidence of anaphylactoid-like reactions during haemodialysis with high-flux dialysis membranes (e.g. AW 69) or undergoing low-density lipoprotein apheresis with dextran sulphate absorption in patients receiving ACE inhibitors. Therefore, this combination should be avoided. In these patients, consideration should be given to use a different type of dialysis, membrane or a different class of medication.

Surgery/Anaesthesia: hypotension may occur in patients undergoing major surgery, or during treatment with anaesthetic agents that are known to lower blood pressure. Captopril will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs, it may be corrected by volume expansion.

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

Diabetic patients: the glycaemia levels should be closely monitored in diabetic patients previously treated with oral antidiabetic drugs or insulin, namely during the first month of treatment with an ACE inhibitor.

Renal function in patient with Heart Failure: Some patients may develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment with captopril. A few patients, generally those with severe pre-existing renal disease, required discontinuation of treatment due to progressively increasing creatinine.

Ethnic differences: as with other angiotensin converting enzyme inhibitors, captopril is apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS): There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors,

angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).
If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.
ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Important information regarding the ingredients this tablet
Lactose: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Potassium sparing diuretics or potassium supplements: ACE inhibitors attenuate diuretic induced potassium loss. Potassium sparring diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. If concomitant use is indicated because of demonstrated hypokalaemia they should be used with caution and with frequent monitoring of serum potassium (see section 4.4).

Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with captopril. Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or potassium containing salt substitutes may lead to significant increases in serum potassium. Care should also be taken when cilazapril is co-administered with other agents that increase serum potassium, such as trimethoprim and cotrimoxazole (trimethoprim/sulfamethoxazole) as trimethoprim is known to act as a potassium sparing diuretic like amiloride. Therefore, the combination of captopril with the above-mentioned drugs is not recommended. If concomitant use is indicated, they should be used with caution and with frequent monitoring of serum potassium.

Diuretics (thiazide or loop diuretics): prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with captopril (see section 4.4). The hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake or by initiating therapy with a low dose of captopril. However, no clinically significant drug interactions have been found in specific studies with hydrochlorothiazide or furosemide.

Ciclosporin
Hyperkalaemia may occur during concomitant use of ACE inhibitors with ciclosporin. Monitoring of serum potassium is recommended.

Heparin
Hyperkalaemia may occur during concomitant use of ACE inhibitors with heparin. Monitoring of serum potassium is recommended.

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

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

Treatments of acute myocardial infarction: Captopril may be used concomitantly with acetylsalicylic acid (at cardiologic doses), thrombolytics, beta-blockers and/or nitrates in patients with myocardial infarction.

Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased risk of lithium toxicity with ACE inhibitors. Use of captopril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4)

Tricyclic antidepressants/ Antipsychotics: ACE inhibitors may enhance the hypotensive effects of certain tricyclic antidepressants and antipsychotics (see section 4.4). Postural hypotension may occur.

Allopurinol, procainamide, cytostatic or immunosuppressive agents: concomitant administration with ACE inhibitors may lead to an increase risk for leucopenia especially when the latter are used at higher than currently recommended doses.

Probenecid*:* The renal clearance of captopril is reduced in the presence of probenecid.

Non-steroidal anti-inflammatory medicinal products: it has been described that non-steroidal anti-inflammatory medicinal products (NSAIDS) (such as Indomethacin, Ibuprofen) and ACE inhibitors exert an additive effects on the increase in serum potassium whereas renal function may decrease. These effects are, in principle, reversible. Rarely, acute renal failure may occur, particularly in patients with compromised renal function such as the elderly or dehydrated. Chronic administration of NSAIDs may reduce the antihypertensive effect of an ACE inhibitor.

Clonidine: It has been suggested that the anti-hypertensive effect of captopril can be delayed when patients treated with clonidine are changed to captopril.

Sympathomimetics: may reduce the antihypertensive effects of ACE inhibitors: patients should be carefully monitored.

Antidiabetics: pharmacological studies have shown that ACE inhibitors, including captopril, can potentiate the blood glucose-reducing effects of insulin and oral antidiabetics such as

sulphonylurea in diabetics. Should this very rare interaction occur, it may be necessary to reduce the dose of the antidiabetics during simultaneous treatment with ACE inhibitors.
Clinical Chemistry: Captopril may cause a false-positive urine test for acetone.

Angiotensin II receptor blockers or aliskiren: Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

Medicines increasing the risk of angioedema Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see section 4.3 and 4.4). Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk for angioedema (see section 4.4).

Co-trimoxazole (trimethoprim/sulfamethoxazole)
Patients taking concomitant co-trimoxazole (trimethoprim/sulfamethoxazole) may be at increased risk for hyperkalaemia (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy:
The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the 2nd and 3rd trimester of pregnancy (see section 4.3 and 4.4). Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.
Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See section 5.3). Should exposure to ACE inhibitors have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).

Breast feeding:
Limited pharmacokinetic data demonstrate very low concentrations in breast milk (see section 5.2). Although these concentrations seem to be clinically irrelevant, the use of Captopril in breastfeeding is not recommended for pre-term infants and for the first few weeks after

delivery, because of the hypothetical risk of cardiovascular and renal effects and because there is not enough clinical experience.

In the case of an older infant, the use of Captopril in a breast-feeding mother may be considered if this treatment is necessary for the mother and the child is observed for any adverse effect.

4.7 Effects on ability to drive and use machines

As with other antihypertensives, the ability to drive and use machines may be reduced, namely at the start of the treatment, or when posology is modified, and also when used in combination with alcohol, but these effects depend on the individual's susceptibility.

4.8 Undesirable effects

Frequency is defined using the following convention: common (≥1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1,000) and very rare (< 1/10,000).

Undesirable effects reported for captopril and/or ACE inhibitor therapy include:

Immune System Disorder:
Frequency not known: Insulin autoimmune syndrome

Blood and lymphatic disorders:
Very rare: neutropenia/agranulocytosis (see section 4.4), pancytopenia particularly in patients with renal dysfunction (see section 4.4), anaemia (including aplastic and haemolytic), thrombocytopenia, lymphadenopathy, eosinophilia, auto-immune disease and/or positive ANA-titres.

Metabolism and nutrition disorders:
Uncommon: decreased appetite
Rare: anorexia
Very rare: hyperkalaemia, hyponatremia, hypoglycaemia (see section 4.4)

Psychiatric disorders:
Common: insomnia
Very rare: confusional state, depression.

Nervous system disorders:
Common: Dysguesia, reversible and self limiting taste impairment and dizziness
Uncommon: headache, paraesthesia
Rare: Somnolence
Very rare: cerebrovascular accident, including stroke cerebrovascular insufficiency, syncope.

Eye disorder:
Very rare: blurred vision

***Cardiac disorders**:*
Uncommon: tachycardia or tachyarrhythmia, arrhythmia, angina pectoris, palpitations.
Very rare: cardiac arrest, cardiogenic shock

Vascular disorders:
Uncommon: Hypotension (see section 4.4), Raynaud's syndrome, flushing, pallor, orthostatic hypotension

Respiratory, thoracic and mediastinal disorders:
Common: dry, irritating (non-productive) cough (see section 4.4) and dyspnoea
Very rare: bronchospasm, rhinitis, allergic alveolitis allergic/eosinophilic pneumonia

Gastrointestinal disorders:
Common: nausea, vomiting, epigastric discomfort, peptic ulcer, dyspepsia, loss of taste (usually reversible on stopping treatment), gastric irritations, abdominal pain, diarrhoea, constipation, dry mouth.
Rare: Weight loss and loss of appetite, stomatitis, resembling aphthous ulcers, intestinal angioedema, mouth ulcers
Very rare: glossitis, pancreatitis.

Hepato-biliary disorders:
Very rare: hepatic function abnormal, cholestasis (including jaundice) hepatitis, including necrosis, hepatic enzyme increased, blood bilirubin increased, transaminase increased, blood alkaline phosphatase increased.

Skin and subcutaneous tissue disorders:
Common: pruritus with or without a rash, rash, and alopecia.
Uncommon: angioedema (see section 4.4)
Very rare: urticaria, Steven Johnson syndrome, erythema multiforme, photosensitivity reaction, erythroderma, pemphigoid and exfoliative dermatitis, psoriasis and psoriasiform dermatitis.

Musculoskeletal, connective tissue and bone disorders:
Very rare: myalgia, arthralgia.

***Renal and urinary disorders**:*
Rare: renal impairment, renal failure, polyuria, oliguria, pollakiuria
Very rare: nephrotic syndrome.

Reproductive system and breast disorders:
Very rare: impotence, erectile dysfunction, gynaecomastia.

***General disorders and administration site conditions**:*
Uncommon: chest pain, fatigue, malaise, asthenia
Very rare: fever

***Investigations**:*
Very rare: proteinuria, eosinophilia, increase of serum potassium, decrease of serum sodium, elevation of BUN, serum creatinine and serum bilirubin, decrease in haemoglobin, haematocrit, leucocytes, thrombocytes, positive antinuclear antibody (ANA) titre, elevated ESR.

Reporting of Suspected Adverse Reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

Symptoms of overdosage are severe hypotension, shock, stupor, bradycardia, electrolyte disturbances and renal failure.

Measures to prevent absorption (e.g. gastric lavage, administration of adsorbents and sodium sulphate within 30 minutes after intake) and hasten elimination should be applied if ingestion is recent. If hypotension occurs, the patient should be placed in the shock position and salt and volume supplementations should be given rapidly. Treatment with angiotensin-II should be considered. Bradycardia or extensive vagal reactions should be treated by administering atropine. The use of a pacemaker may be considered.

Captopril may be removed from adult circulation by haemodialysis. Captopril is not adequately cleared by peritoneal dialysis.

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, ACE inhibitors, plain,
ATC code: C09AA01

Captopril is a highly specific, competitive inhibitor of angiotensin-I converting enzyme (ACE inhibitors).

The beneficial effects of ACE inhibitors appear to result primarily from the suppression of the plasma renin-angiotensin-aldosterone system. Renin is an endogenous enzyme synthesized by the kidneys and released into the circulation where it converts angiotensinogen to angiotensin-I a relatively inactive decapeptide. Angiotensin-I is then converted by angiotensin converting enzyme, a peptidyldipeptidase, to angiotensin-II. Angiotensin-II is a potent vasoconstrictor responsible for arterial vasoconstriction and increased blood pressure, as well as for stimulation of the adrenal gland to secrete aldosterone. Inhibition of ACE results in decreased plasma angiotensin-II, which leads to decreased vasopressor activity and to reduced aldosterone secretion. Although the latter decrease is small, small increases in serum potassium concentrations may occur, along with sodium and fluid loss. The cessation of the

negative feedback of angiotensin-II on the rennin secretion results in an increase of the plasma renin activity.

Another function of the converting enzyme is to degrade the potent vasodepressive kinin peptide bradykinin to inactive metabolites. Therefore, inhibition of ACE results in an increased activity of circulating and local kallikrein-kinin-system which contributes to peripheral vasodilation by activating the prostaglandin system; it is possible that this mechanism is involved in the hypotensive effect of ACE inhibitors and is responsible for certain adverse reactions.

Reductions of blood pressure are usually maximal 60 to 90 minutes after oral administration of an individual dose of captopril. The duration of effect is dose related. The reduction in blood pressure may be progressive, so to achieve maximal therapeutic effects, several weeks of therapy may be required. The blood pressure lowering effects of captopril and thiazide-type diuretics are additive.
In patients with hypertension, captopril causes a reduction in supine and erect blood pressure, without inducing any compensatory increase in heart rate, nor water and sodium retention.

In haemodynamic investigations, captopril caused a marked reduction in peripheral arterial resistance. In general there were no clinically relevant changes in renal plasma flow or glomerular filtration rate. In most patients, the antihypertensive effect began about 15 to 30 minutes after oral administration of captopril; the peak effect was achieved after 60 to 90 minutes. The maximum reduction in blood pressure of a defined captopril dose was generally visible after three to four weeks.

In the recommended daily dose, the antihypertensive effect persists even during long-term treatment. Temporary withdrawal of captopril does not cause any rapid, excessive increase in blood pressure (rebound). The treatment of hypertension with captopril leads also to a decrease in left ventricular hypertrophy.

Haemodynamic investigations in patients with heart failure showed that captopril caused a reduction in peripheral systemic resistance and a rise in venous capacity. This resulted in a reduction in pre-load and after-load of the heart (reduction in ventricular filling pressure). In addition, rises in cardiac output, work index and exercise capacity have been observed during treatment with captopril. In a large, placebo-controlled study in patients with left ventricular dysfunction (LVEF $\leq$40%) following myocardial infarction, it was shown that captopril (initiated between the 3rd to the 16th day after infarction) prolonged the survival time and reduced cardiovascular mortality. The latter was manifested as a delay in the development of symptomatic heart failure and a reduction in the necessity for hospitalisation due to heart failure compared to placebo. There was also a reduction in re-infarction and in cardiac revascularisation procedures and/or in the need for additional medication with diuretics and/or digitalis or an increase in their dosage compared to placebo.

A retrospective analysis showed that captopril reduced recurrent infarcts and cardiac revascularisation procedures (neither were target criteria of the study)
Another large, placebo-controlled study in patients with myocardial infarction showed that captopril (given within 24 hours of the event and for duration of one month) significantly

reduced overall mortality after 5 weeks compared to placebo. The favourable effect of captopril on total mortality was still detectable even after one year. No indication of a negative effect in relation to early mortality on the first day of treatment was found.

Captopril cardioprotection effects are observed regardless of the patient's age or gender, location of the infarction and concomitant treatments with proven efficacy during the post-infarction period (thrombolytic agents, beta-blockers and acetylsalicylic acid)

Type I diabetic nephropathy

In a placebo-controlled, multicentre double blind clinical trial in insulin-dependent (Type I) diabetes with proteinuria, with or without hypertension (simultaneous administration of other antihypertensives to control blood pressure was allowed), captopril significantly reduced (by 51%) the time to doubling of the baseline creatinine concentration compared to placebo; the incidence of terminal renal failure (dialysis, transplantation) or death was also significantly less common under captopril than under placebo (51%). In patients with diabetes and microalbuminuria, treatment with captopril reduced albumin excretion within two years. 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.

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.
ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

5.2 Pharmacokinetic properties

Absorption
The average minimal absorption is approximately 75%. Peak plasma concentrations are reached within 60-90 minutes. The presence of food in gastrointestinal tract reduces absorption by about 30-40%. Approximately 25-30% of the circulating drug is bound to plasma proteins.

Biotransformation
Captopril is orally active agent that dose not require biotransformation for activity.

Elimination
The apparent elimination half-life of unchanged captopril in blood is about 2 hours. Greater than 95% of the absorbed dose is eliminated in the urine within 24 hours; 40-50% is unchanged drug and the remainder are inactive disulphide metabolites (captopril disulphide and captopril cysteine disulphide). Impaired renal function could result in drug accumulation. Therefore, in patients with impaired renal function the dose should be reduced and/or dosage interval prolonged (see section 4.2)
Studies in animals indicate that captopril does not cross the blood-brain barrier to any significant effect.

Lactation
In the report of twelve women taking oral captopril 100mg 3 times daily, the average peak milk level was 4.7µg/L and occurred 3.8 hours after the dose. Based on these data, the maximum daily dosage that a nursing infant would receive is less than 0.002% of the maternal daily dosage.

5.3 Preclinical safety data

Animal studies performed during organogenesis with captopril have not shown any teratogenic effect but captopril has produced foetal toxicity in several species, including foetal mortality during late pregnancy, growth retardation and postnatal mortality in the rat. Preclinical data reveal no other specific hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicology, genotoxicity and carcinogenicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Microcrystalline cellulose,
Maize starch,
Lactose monohydrate,
Stearic acid.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package

6.5 Nature and contents of container

Al/PVC blisters.
Pack sizes: 28 and 56 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

None stated

7 MARKETING AUTHORISATION HOLDER

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