SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Captopril 25 mg/5 ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of Captopril 25 mg/5 ml Oral Solution contains 5 mg captopril.

Each 5 ml of Captopril 25 mg/5 ml Oral Solution contains 25 mg captopril.

Excipient(s) with known effects:

This medicinal product contains 0.192 mmol (or 4.40 mg) sodium per 5 mL.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Oral solution

Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Captopril oral solution is indicated for:

Hypertension: the treatment of essential hypertension.

Heart Failure: for the treatment of chronic heart failure.

Myocardial Infarction:

- short-term (4 weeks) treatment: Captopril Oral Solution is indicated in any clinically stable patient within the first 24 hours of an infarction.

- long-term prevention of symptomatic heart failure: indicated in clinically stable patients with asymptomatic left ventricular dysfunction.

Type I Diabetic Nephropathy: indicated for the treatment of macroproteinuric diabetic nephropathy in patients with type I diabetes. (See section 5.1).

Captopril oral solution 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 150 mg.
Captopril oral solution may be taken before, during and after meals.
Hypertension: 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 oral solution may be used alone or with other antihypertensive agents, especially thiazide diuretics. A once-daily dosing regimen may be appropriate when concomitant antihypertensive medication such as thiazide diuretics is added (see sections 4.3, 4.4, 4.5 and 5.1).
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 50 mg per day in one or two doses and if necessary to 100 mg per day in one or two doses.
Heart failure: treatment with captopril for heart failure should be initiated under close medical supervision. The usual starting dose is 6.25 mg - 12.5 mg BID or TID. Titration to the maintenance dose (75 - 150 mg per day) should be carried out based on patient's response, clinical status and tolerability, up to a maximum of 150 mg 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 6.25 mg test dose should be administered, with a 12.5 mg dose being administered 2 hours afterwards and a 25 mg dose 12 hours later. From the following day, captopril should be administered in a 100 mg/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 75 mg 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 6.25 mg followed by 12.5 mg 3 times daily for 2 days and then 25 mg 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 150 mg 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 of captopril is 75-100 mg in divided doses. If additional lowering of blood pressure is desired, additional antihypertensive medications may be added.
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/1.73 m^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 patients: 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 dysfunctions (see above 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 0.3 mg/kg body weight to be divided in 3 equal doses daily. For patients requiring special precautions (children with renal dysfunction, premature infants, new-borns and infants,

because their renal function is not the same as 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 only

4.3 Contraindications

- Hypersensitivity to captopril, to any other ACE inhibitor or to any of the excipients (see section 6.1)
- History of angioedema associated with previous ACE inhibitor therapy
- Hereditary/idiopathic angioneurotic oedema
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- Use in patients with aortic stenosis or outflow tract obstruction.
- Use in patients with bilateral renal artery stenosis in a single functioning kidney.
- The concomitant use of captopril with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2) (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

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

In cases of renal impairment (creatinine clearance ≤40 ml/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.

Angioedema

Angioneurotic oedema of the extremities, face, lips, mucous membranes, tongue, glottis and/or larynx may occur in patients treated with ACE inhibitors particularly during the first week of 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. Emergency therapy should be instituted. 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 patient airway, should be administered promptly. 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 contraindications)

Intestinal angioedema:

Intestinal angioedema has also been reported very 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 undesirable effects).

Hypersensitivity/angioedema:

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.

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.

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.

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.

Serum potassium

ACE inhibitors can elevate serum potassium because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. However, in patients with diabetes mellitus, impaired renal function and/or in patients taking potassium supplements (including salt substitutes), potassium-sparing diuretics, trimethoprim or co-trimoxazole 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).

Lithium

The combination of lithium and captopril is not recommended due to the potentiation of lithium toxicity (see section 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 and 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 collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. 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 (e.g. 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 1 g 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.

Patients with prior renal disease should have urinary protein estimations (dip-stick on first morning urine) prior to treatment, and periodically thereafter.

Anaphylactoid reactions during desensitisation

Sustained life-threatening anaphylactoid reactions have been rarely reported for patients undergoing desensitising 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 inhibitors undergoing such desensitisation procedures.

Anaphylactoid reactions during high-flux dialysis / lipoprotein apheresis membrane exposure

Anaphylactoid reactions have been reported in patients haemodialysed with high-flux dialysis membranes or undergoing low-density lipoprotein apheresis with dextran sulphate absorption. In these patients, consideration should be given to using 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. If hypotension occurs, it may be corrected by volume expansion.

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 patients 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.

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.

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.

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)

Paediatric Population

Neonates

The neonatal response to treatment with ACE inhibitors is very variable, and some neonates develop profound hypotension with even small doses; a test-dose should be used initially and increased cautiously. Adverse effects such as apnoea, seizures, renal failure, and severe unpredictable hypotension are very common in the first month of life and it is therefore recommended that ACE inhibitors are used with caution, particularly in preterm neonates.

Oliguria is a risk in premature patients treated with captopril.

Routine monitoring of infants on ACE inhibitors should include renal function tests, blood pressure and transcutaneous oxygen saturation measurements.

Older Children

As with neonates, older children can experience severe hypotension on administration of captopril. A small initial test dose should be administered with the patient supine, in order to avoid severe hypotension and tachycardia. As with adults hyperkalaemia may occur in conjunction with potassium sparing diuretics. Routine monitoring should include test for renal function. Dosages should be reduced in patients with impaired renal function.

Leukopenia has been reported in children with renal impairment treated with captopril.

Sodium

Captopril 25 mg/5 ml Oral Solution contains 4.4 mg (0.19 mmol) sodium per 5 ml, equivalent to 0.22% of the WHO recommended maximum daily intake of 2 g sodium for an adult. The maximum daily dose of 30 mL (150 mg captopril) contains 26.4 .mg (1.15 mmol) sodium, equivalent to 1.3% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Captopril Oral Solution is available in two strengths 5 mg/5 ml and 25 mg/5 ml; caution is advised in ensuring that the correct strength is given to the patient. The doctor should prescribe the most appropriate strength based upon the clinical requirements of the patient (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes: 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 captopril is co-administered with other agents that increase serum potassium, such as trimethoprim and co-trimoxazole (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.

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, should be used with caution.

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

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 immuno-suppressive agents: concomitant administration with ACE inhibitors may lead to an increased risk for leucopenia especially when the latter are used at higher than currently recommended doses.

Non-steroidal anti-inflammatory medicinal products: it has been described that non-steroidal anti-inflammatory medicinal products (NSAIDs) and ACE inhibitors exert an additive effect 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.

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 antidiabetic during simultaneous treatment with ACE inhibitors.
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-trimaxozole (trimethoprim/sulfamethoxazole)

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

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.

Clinical Chemistry

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

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).

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 second and third trimesters of pregnancy (see sections 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 fetotoxicity (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).

Breastfeeding

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 Oral Solution in breast-feeding is not recommended for preterm 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 Oral Solution 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.

Fertility

No human fertility data are available. No evidence of impaired fertility was detected in animal studies (see section 5.3).

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

The table below lists adverse reactions reported with Captopril, ranked under the following frequency classification:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions with Captopril in clinical trials and post-marketing experience

Frequency	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not Known**
System organ class					
Blood and lymphatic system disorders				Neutropenia/ agranulocytosis, pancytopenia particularly in patients with renal dysfunction, anaemia (including aplastic and haemolytic), thrombocytopenia, lymphadenopathy, eosinophilia, auto-immune diseases and/or positive ANA-titres	
Metabolism and nutrition disorders		Decreased appetite		Hyperkalaemia, hyponatremia, hypoglycemia	
Psychiatric disorders	Sleep disorders			Confusion, depression	
Nervous system disorders	Taste impairment, dizziness	Headache, paraesthesia	Drowsiness	Cerebrovascular accident, cerebrovascular insufficiency, syncope	
Eye disorders				Blurred vision	
Cardiac disorders		Tachycardia or arrhythmia, angina pectoris, palpitations		Cardiac arrest, cardiogenic shock	
Vascular Disorders		Hypotension, Raynaud syndrome, flush, pallor, orthostatic hypotension			

Frequency **System organ class**	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not Known**
Respiratory, thoracic and mediastinal disorders	Dry, irritating (non-productive) cough and dyspnoea			Bronchospasm, rhinitis, allergic alveolitis/ eosinophilic pneumonia	
Gastrointestinal disorders	Nausea, vomiting, gastric irritations, abdominal pain, diarrhoea, constipation, dry mouth, peptic ulcer, dyspepsia		Intestinal angioedema, Stomatitis/ aphthous stomatitis	glossitis, pancreatitis	
Hepatobiliary disorders				Hepatic function abnormal, cholestasis, jaundice, hepatitis, hepatic necrosis, elevated liver enzymes and blood bilirubin, transaminase increase, blood alkaline phosphatase increase	
Skin and subcutaneous tissue disorders	Pruritus with or without a rash, rash, and alopecia	Angioedema		Urticaria, Stevens Johnson syndrome, erythema multiforme, photosensitivity reaction, erythroderma multiforme, pemphigoid reactions and exfoliative dermatitis	

Frequency **System organ class**	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not Known**
Musculoskeletal and connective tissue disorders				Myalgia, arthralgia	
Renal and urinary disorders			Renal impairment, renal failure, polyuria, oliguria, increased urine frequency (pollakiuria)	Nephrotic syndrome	
Reproductive system and breast disorders				Impotence, gynaecomastia	
General disorders and administration site conditions		Chest pain, fatigue, malaise, asthenia		Fever	
Investigations				Proteinuria, eosinophilia, increase of serum potassium, decrease of serum sodium, elevation of BUN, serum creatinine and serum bilirubin, decreases in haemoglobin, haematocrit, leucocytes, thrombocytes and platelet count, positive ANA-titre, elevated ESR	
Immune System Disorders					Insulin autoimmune syndrome

Paediatric Population

The major adverse events seen in the paediatric population were persistent dry cough, hyperkalemia, angioedema, decreased GFR, hypotension, neutropenia, impaired hepatic function and renal disorders.

The reactions most frequently observed during captopril therapy were headache, tachycardia, vomiting, postural symptoms, anaemia, rash and anorexia.

Adverse effects such as apnoea, seizures, renal failure, and severe unpredictable hypotension are very common in the first month of life and it is therefore recommended that ACE inhibitors are used with caution, particularly in preterm neonates **(see section 4.4 Special Warnings and Precautions for use, Paediatric Population).**

Oliguria is a risk in premature patients treated with captopril **(see section 4.4 Special Warnings and Precautions for use, Paediatric Population).**

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.

After ingestion of an overdose, the patient should be kept under close supervision, preferably in an intensive care unit. Serum electrolytes and creatinine should be monitored frequently, as well as blood pressure. Therapeutic measures depend on the nature and severity of the symptoms.

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. The use of high-flux polyacrylonitrile membranes should be avoided. Naloxone has been used both successfully and unsuccessfully to reverse hypotension associated with captopril overdose. Captopril is not adequately cleared by peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 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 synthesised 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 renin 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

Captopril is an orally active agent that does not require biotransformation for activity. The average minimal absorption is approximately 75%. Peak plasma concentrations are reached within 60-90 minutes. The presence of food in the gastrointestinal tract reduces absorption by about 30-40%. Approximately 25-30% of the circulating drug is bound to plasma proteins.

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).

Bioequivalence of Captopril Oral Solution has been demonstrated to the reference tablet in a single dose, randomised, crossover bioequivalence study comparing Captopril 25mg/5ml Oral Solution to the reference Capoten 25mg Tablet.

Studies in animals indicate that captopril does not cross the blood-brain barrier to any significant extent.

Lactation

In the report of twelve women taking oral captopril 100 mg 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 fetal toxicity in several species, including fetal mortality during late pregnancy, growth retardation and postnatal mortality in the rat. Captopril had no adverse effects on fertility of male and female rats at oral doses up to 1800 mg/kg/day. 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

Citric acid monohydrate (E330)

Sodium citrate dihydrate (E331)

Sodium benzoate (E211)

Disodium edetate (E386)

Purified water

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened: 12 months

After first opening: 28 days

6.4 Special precautions for storage

Do not store above 25°C.

Do not freeze.

6.5 Nature and contents of container

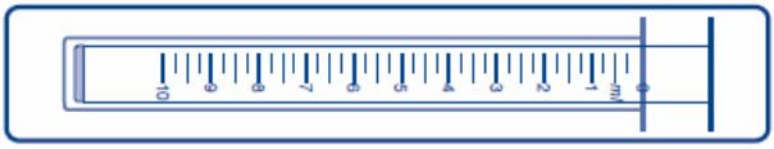
Amber glass bottle containing 100 ml, closed with a tamper evident, child resistant closure (HDPE/Polypropylene cap with tamper evident band and expanded polyethylene liner).

The bottle is supplied with a CE-marked 10 ml graduated dosing pipette, and a separate 'bung' adaptor which is fitted to the neck of the bottle at first use (i.e. after opening), to ensure proper use of the pipette. The dosing pipette consists of an LDPE barrel and a plunger made from polystyrene (PS) with a LDPE piston. The bottle adaptor is made from LDPE.

6.6 Special precautions for disposal

Method of administration:

Each carton will contain a 10 ml graduated dosing pipette and a dosing adaptor.



10 ml pipette, each numbered section is 1 ml and the smaller increments are 0.25 ml.

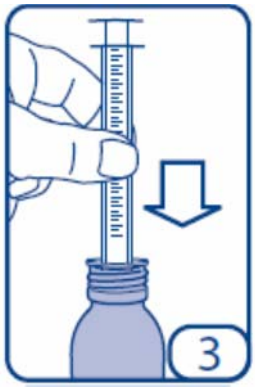
Captopril 25 mg/5 ml Oral Solution: 1 ml is equivalent to 5 mg and 0.25 ml is equivalent to 1.25 mg

Instructions for using the dosing pipette

• Open the bottle: press the cap and turn it anticlockwise (figure 1)

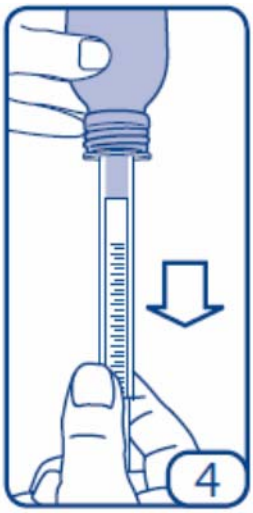
• On using the bottle for the first time, the pipette adaptor must be fitted. It will then stay in place for future doses. Holding the bottle, take the plastic pipette adaptor from the box and insert the adaptor into the bottle neck (figure 2). Ensure it is well fixed.

• Take the pipette and put it in the adaptor opening (figure 3).



• Hold the pipette in place and turn the bottle upside down.

• Still holding the pipette in place, pull the piston down to the graduation mark corresponding to the quantity in millilitres (ml) prescribed by your doctor (figure 4).



• Turn the bottle the right way up. Remove the pipette from the adaptor (figure 5).

• Administer the contents of the pipette into the mouth by pushing the piston to the bottom of the pipette and ensure the medicine is swallowed.

Do not remove the adaptor from the bottle neck, it is intended to stay in place. Close the bottle with the plastic screw cap.

Wash the pipette with warm water. Dry it with a clean paper towel and replace into the box with your medicine.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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