1.3 PRODUCT INFORMATION

1.3.1 Summary of Product Characteristics (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

1.1 Name of the Medicinal Product: -
Generic Name: Lisinopril Tablets USP 10 mg

1.2 Strength
10 mg

1.3 Pharmaceutical Form
Uncoated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains-
Lisinopril (Dihydrate) USP
Eq.to. Anhydrous Lisinopril .....10 mg
Excipients.....q.s.

3. PHARMACEUTICAL FORM

Uncoated Tablets

4. Clinical particulars

4.1 Therapeutic indications

• Hypertension: Treatment of hypertension.
• Heart failure: Treatment of symptomatic heart failure.
• Acute myocardial infarction: Short-term (6 weeks) treatment of haemodynamically stable patients within 24 hours of an acute myocardial infarction.
• Renal complications of diabetes mellitus: Treatment of renal disease in hypertensive patients with Type 2 diabetes mellitus and incipient nephropathy.

4.2 Posology and method of administration

Posology
Lisinopril should be administered orally in a single daily dose. As with all other medication taken once daily, lisinopril should be taken at approximately the same time each day. The absorption of lisinopril tablets is not affected by food.
The dose should be individualized according to patient profile and blood pressure response (see section 4.4).
Hypertension
Lisinopril may be used as monotherapy or in combination with other classes of antihypertensive medicinal products (see sections 4.3, 4.4, 4.5 and 5.1).
• Starting dose
In patients with hypertension the usual recommended starting dose is 10mg. Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, renovascular

hypertension, salt and or volume depletion, cardiac decompensation, or severe hypertension) may experience an excessive blood pressure fall following the initial dose. A starting dose of 2.5-5mg is recommended in such patients and the initiation of treatment should take place under medical supervision. A lower starting dose is required in the presence of renal impairment (see Table 1 below).

• Maintenance dose

The usual effective maintenance dosage is 20mg administered in a single daily dose. In general if the desired therapeutic effect cannot be achieved in a period of 2 to 4 weeks on a certain dose level, the dose can be further increased. The maximum dose used in long-term, controlled clinical trials was 80mg/day.

• Diuretic -treated patients

Symptomatic hypotension may occur following initiation of therapy with lisinopril. This is more likely in patients who are being treated currently with diuretics. Caution is recommended therefore, since these patients may be volume and/or salt depleted. If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with lisinopril. In hypertensive patients in whom the diuretic cannot be discontinued, therapy with lisinopril should be initiated with a 5mg dose. Renal function and serum

potassium should be monitored. The subsequent dosage of lisinopril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed (see section 4.4 and section 4.5).

• Dosage adiustment in renal impairment

Dosage in patients with renal impairment should be based on creatinine clearance as outlined in Table 1 below.

Table 1 Dosage adjustment in renal impairment.

Creatinine Clearance (ml/min)	Starting Dose (mg/day)
Less than 10 ml/min (including patients on dialysis)	2.5 mg*
10-30 ml/min	2.5-5mg
31-80ml/min	5-10mg

* Dosage and/or frequency of administration should be adjusted depending on the blood pressure response.

The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Use in Hypertensive Paediatric Patients aged 6-16 years

The recommended initial dose is 2.5 mg once daily in patients 20 to <50 kg, and 5 mg once daily in patients ≥50 kg. The dosage should be individually adjusted to a maximum of 20 mg daily in patients weighing 20 to <50 kg, and 40 mg in patients ≥50kg. Doses above 0.61 mg/kg (or in excess of 40 mg) have not been studied in paediatric patients (see section 5.1). In children with decreased renal function, a lower starting dose or increased dosing interval should be considered.

Heart failure

In patients with symptomatic heart failure, lisinopril should be used as adjunctive therapy to diuretics and, where appropriate, digitalis or beta-blockers. Lisinopril may be initiated at a starting dose of 2.5mg once a day, which should be administered under medical supervision to determine the initial effect on the blood pressure. The dose of lisinopril should be increased:

• By increments of no greater than 10mg
• At intervals of no less than 2 weeks
• To the highest dose tolerated by the patient up to a maximum of 35mg once daily.
Dose adjustment should be based on the clinical response of individual patients.
Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy should have these conditions corrected, if possible, prior to therapy with lisinopril. Renal function and serum potassium should be monitored (see section 4.4).

Acute myocardial infarction

Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin, and beta-blockers. Intravenous or transdermal glyceryl trinitrate may be used together with lisinopril.
• Starting dose (first 3 days after infarction)
Treatment with lisinopril may be started within 24 hours of the onset of symptoms. Treatment should not be started if systolic blood pressure is lower than 100mm Hg. The first dose of lisinopril is 5mg given orally, followed by 5mg after 24 hours, 10mg after 48 hours and then 10mg once daily. Patients with a low systolic blood pressure (120mm Hg or less) when treatment is started or during the first 3 days after the infarction should be given a lower dose - 2.5mg orally (see section 4.4).
In cases of renal impairment (creatinine clearance <80 ml/min), the initial lisinopril dosage should be adjusted according to the patient's creatinine clearance (see Table 1).
• Maintenance dose
The maintenance dose is 10mg once daily. If hypotension occurs (systolic blood pressure less than or equal to 100mm Hg) a daily maintenance dose of 5mg may be given with temporary reductions to 2.5mg if needed. If prolonged hypotension occurs (systolic blood pressure less than 90mm Hg for more than I hour) lisinopril should be withdrawn.
Treatment should continue for 6 weeks and then the patient should be re-evaluated. Patients who develop symptoms of heart failure should continue with lisinopril (see section 4.2).

Renal complications of diabetes mellitus

In hypertensive patients with type 2 diabetes and incipient nephropathy, the dose is 10mg lisinopril once daily which can be increased to 20mg once daily, if necessary, to achieve a sitting diastolic blood pressure below 90mm Hg
In cases of renal impairment (creatinine clearance <80 ml/min), the initial lisinopril dosage should be adjusted according to the patient's creatinine clearance (see Table 1).

Paediatric population

There is limited efficacy and safety experience in hypertensive children >6 years old,
but no experience in other indications (see section 5.1). Lisinopril is not recommended in children in other indications than hypertension.
Lisinopril is not recommended in children below the age of 6, or in children with severe renal impairment (GFR <30ml/min/1.73m2) (see section 5.2).

Use in the elderly

In clinical studies, there was no age-related change in the efficacy or safety profile of the drug. When advanced age is associated with decrease in renal function, however, the guidelines set out in Table 1 should be used to determine the starting dose of lisinopril. Thereafter, the dosage should be adjusted according to the blood pressure response.

Use in kidney transplant patients

There is no experience regarding the administration of lisinopril in patients with recent kidney transplantation. Treatment with lisinopril is therefore not recommended.
Method of Administration
For oral administration

4.3 Contraindications
• Hypersensitivity to the active substance, or to any of the excipients listed in section 6.1 or any other angiotensin converting enzyme (ACE) inhibitor.
• History of angioedema associated with previous ACE inhibitor therapy.
• Hereditary or idiopathic angioedema.
• Second and third trimesters of pregnancy (see section 4.4 and 4.6).
• The concomitant use of Lisinopril with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73m^2) (see section 4.5 and 5.1).
• Concomitant use with sacubitril/valsartan therapy. Lisinopril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan

4.4 Special warnings and precautions for use
Symptomatic hypotension
Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving lisinopril, hypotension is more likely to occur if the patient has been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin dependent hypertension (see section 4.5 and section 4.8). In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored. Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.
If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.
In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with lisinopril. This effect is anticipated and is not usually a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of lisinopril may be necessary.
Hypotension in acute myocardial infarction
Treatment with lisinopril must not be initiated in acute myocardial infarction patients who are at risk of further serious haemodynamic deterioration after treatment with a vasodilator. These are patients with systolic blood pressure of 100mm Hg or lower or those in cardiogenic shock. During the first 3 days following the infarction, the dose should be reduced if the systolic blood pressure is 120mm Hg or lower. Maintenance doses should be reduced to 5mg or temporarily to 2.5mg if systolic blood pressure is 100mm Hg or lower. If hypotension persists (systolic blood pressure less than 90mm Hg for more than 1 hour) then lisinopril should be withdrawn.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

As with other ACE inhibitors, lisinopril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

Renal function impairment

In cases of renal impairment (creatinine clearance <80 ml/min), the initial lisinopril dosage should be adjusted according to the patient's creatinine clearance (see Table 1 in section 4.2) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine is part of normal medical practice for these patients.

In patients with heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.

In some patients with bilateral renal artery stenosis or with a stenosis of the artery to a solitary kidney, who have been treated with angiotensin converting enzyme inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of lisinopril therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when lisinopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or lisinopril may be required.

In acute myocardial infarction, treatment with lisinopril should not be initiated in patients with evidence of renal dysfunction, defined as serum creatinine concentration exceeding 177 micromol/l and/or proteinuria exceeding 500mg/24h. If renal dysfunction develops during treatment with lisinopril (serum creatinine concentration exceeding 265 micromol/l or a doubling from the pre-treatment value) then the physician should consider withdrawal of lisinopril.

Hypersensitivity/Angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely in patients treated with angiotensin converting enzyme inhibitors, including lisinopril. This may occur at any time during therapy. In such cases, lisinopril should be discontinued promptly and appropriate treatment and monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patients. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient. Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx, are likely to experience airway obstruction, especially those with a history of airway surgery. In such cases emergency therapy should be administered promptly. This may include the administration of adrenaline (epinephrine) and/or the maintenance of a patient airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

Angiotensin converting enzyme inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

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).

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 lisinopril. Treatment with lisinopril 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.

Anaphylactoid reactions in haemodialysis patients

Anaphylactoid reactions have been reported in patients dialysed with high flux membranes (e.g. AN69) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

Rarely, patients receiving ACE inhibitors during low-density lipoproteins (LDL) apheresis with dextran sulfate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Desensitisation

Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have sustained anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld but they have reappeared upon inadvertent re-administration of the medicinal product.

Hepatic failure

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

Neutropenia/Agranulocytosis

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Neutropenia and agranulocytosis are reversible after discontinuation of the ACE inhibitor. Lisinopril 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 lisinopril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

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.

Race

ACE inhibitors cause a higher rate of angioedema in black patients than in non-black patients. As with other ACE inhibitors, lisinopril may be less effective in lowering blood pressure in black patients than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Cough

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, lisinopril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

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, diabetes mellitus and/or in patients taking potassium supplements (including salt substitutes), potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), other drugs associated with increase in serum potassium (e.g. heparin, 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).

Diabetic patients

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor (see section 4.5).

Lithium

The combination of lithium and lisinopril is generally not recommended (see section 4.5).

Pregnancy and lactation

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

4.5 Interaction with other medicinal products and other forms of interaction

Lisinopril can interact with the following drugs or groups of drugs:

Antihypertensive agents:

When Lisinopril is combined with other antihypertensive agents (e.g. glyceryl trinitrate and other nitrates, or other vasodilators) additive falls in blood pressure may occur.

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 treatment of ACE inhibitors with mammalian target of rapamycin (mTOR) inhibitors (e.g. temsirolimus, sirolimus, everolimus) or neutral endopeptidase (NEP) inhibitors (e.g. racecadotril), vildagliptin or tissue plasminogen activator may increase the risk of angioedema (see section 4.4).

Diuretics:

When a diuretic is added to the therapy of a patient receiving lisinopril the antihypertensive effect is usually additive.

Patients already on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure when lisinopril is added. The possibility of symptomatic hypotension with lisinopril can be minimised by discontinuing the diuretic prior to initiation of treatment with lisinopril (see section 4.2 and 4.4).

Potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutes and other drugs that may increase serum potassium levels:

Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with lisinopril. Use of potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes, particularly in patients with impaired renal function, may lead to significant increases in serum potassium. Care should also be taken when lisinopril 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 lisinopril 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.

If Lisinopril is given with a potassium-losing diuretic, diuretic-induced hypokalaemia may be ameliorated.

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.

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 lithium toxicity with

ACE inhibitors. Use of lisinopril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

Non steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid ≥ 3G/day:

When ACE inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. These effects are usually reversible. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Gold:

Nitritoid reactions (symptoms of vasodilatation including flushing, nausea, dizziness and hypotension, which can be very severe) following injectable gold (for example, sodium aurothiomalate) have been reported more frequently in patients receiving ACE inhibitor therapy.

Tricyclic antidepressants / Antipsychotics /Anaesthetics

Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section 4.4).

Sympathomimetics:

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Antidiabetics:

Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicinal products (insulins, oral hypoglycaemic agents) may cause an increased blood glucose lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates:

Lisinopril may be used concomitantly with acetylsalicylic acid (at cardiologic doses), thrombolytics, beta-blockers and/or nitrates.

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 trimester 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 foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation)

and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See section 5.3.) Should exposure to ACE inhibitor 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

Because no information is available regarding the use of Lisinopril during breastfeeding, Lisinopril is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

4.7 Effects on ability to drive and use machines

When driving vehicles or operating machines it should be taken into account that occasionally dizziness, tiredness or confusion may occur.

4.8 Undesirable effects

The following undesirable effects have been observed and reported during treatment with lisinopril and other ACE inhibitors with the following frequencies:

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

• Blood and the lymphatic system disorders:

Rare: decreases in haemoglobin, decreases in haematocrit.

Very rare: bone marrow depression, anaemia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis (see section 4.4), haemolytic anaemia, lymphadenopathy, autoimmune disease.

• Immune system disorders

Not known: anaphylactic/anaphylactoid reaction

• Metabolism and nutrition disorders

Very rare: hypoglycaemia.

• Nervous system and psychiatric disorders:

Common: dizziness, headache.

Uncommon: mood alterations, paraesthesia, vertigo, taste disturbance, sleep disturbances, hallucinations.

Rare: mental confusion, olfactory disturbance.

Not known: syncope, depressive symptoms.

• Cardiac and vascular disorders:

Common: orthostatic effects (including hypotension).

Uncommon: myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see section 4.4), palpitations, tachycardia. Raynaud's phenomenon.

• Respiratory, thoracic and mediastinal disorders:

Common: cough.

Uncommon: rhinitis.

Very rare: bronchospasm, sinusitis, allergic alveolitis/eosinophilic pneumonia.

• Gastrointestinal disorders:

Common: diarrhoea, vomiting.

Uncommon: nausea, abdominal pain and indigestion.

Rare: dry mouth.

Very rare: pancreatitis, intestinal angioedema, hepatitis- either hepatocellular or cholestatic, jaundice and hepatic failure (see section 4.4).
• Skin and subcutaneous tissue disorders:
Uncommon: rash, pruritus
Rare: urticaria, alopecia, psoriasis, hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx (see section 4.4).
Very rare: sweating, pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme, cutaneous pseudolymphoma.
A symptom complex has been reported which may include one or more of the following: fever, vasculitis, myalgia, arthralgia/arthritis, a positive antinuclear antibodies (ANA), elevated red blood cell sedimentation rate (ESR), eosinophilia and leucocytosis, rash, photosensitivity or other dermatological manifestations may occur.
• Renal and urinary disorders:
Common: renal dysfunction.
Rare: uraemia, acute renal failure.
Very rare: oliguria/anuria.
• Endocrine Disorders:
Rare: syndrome of inappropriate antidiuretic hormone secretion (SIADH)
• Reproductive system and breast disorders:
Uncommon: impotence.
Rare: gynaecomastia.
• General disorders and administration site conditions:
Uncommon: fatigue, asthenia.
• Investigations:
Uncommon: increases in blood urea, increases in serum creatinine, increases in liver enzymes, hyperkalaemia
Rare: increases in serum bilirubin, hyponatraemia.
Safety data from clinical studies suggest that lisinopril is generally well tolerated in hypertensive paediatric patients, and that the safety profile in this age group is comparable to that seen in adults.

4.9 Overdose

Limited data are available for overdose in humans. Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough.
The recommended treatment of overdose is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. If ingestion is recent, take measures aimed at eliminating Lisinopril (e.g. emesis, gastric lavage, administration of absorbents and sodium sulfate). Lisinopril may be removed from the general circulation by haemodialysis. Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored frequently.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin converting enzyme inhibitors, ATC code: C09AA03

Mechanism of action

Lisinopril is a peptidyl dipeptidase inhibitor. It inhibits the angiotensin converting enzyme (ACE) that catalyses the conversion of angiotensin I to the vasoconstrictor peptide, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased concentrations of angiotensin II which results in decreased vasopressor activity and reduced aldosterone secretion. The latter decrease may result in an increase in serum potassium concentration.

Pharmacodynamic effects

Whilst the mechanism through which lisinopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, lisinopril is antihypertensive even in patients with low renin hypertension. ACE is identical to kininase II, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodilatory peptide, play a role in the therapeutic effects of lisinopril remains to be elucidated.

Clinical efficacy and safety

The effect of lisinopril on mortality and morbidity in heart failure has been studied by comparing a high dose (32.5mg or 35mg once daily) with a low dose (2.5mg or 5mg once daily). In a study of 3l64 patients, with a median follow up period of 46 months for surviving patients, high dose lisinopril produced a 12% risk reduction in the combined endpoint of all-cause mortality and all-cause hospitalisation ($p = 0.002$) and an 8% risk reduction in all-cause mortality and cardiovascular hospitalisation ($p = 0.036$) compared with low dose. Risk reductions for all-cause mortality (8%; $p = 0.128$) and cardiovascular mortality (10%; $p = 0.073$) were observed. In a post-hoc analysis, the number of hospitalisations for heart failure was reduced by 24% ($p=0.002$) in patients treated with high-dose lisinopril compared with low dose. Symptomatic benefits were similar in patients treated with high and low doses of lisinopril.

The results of the study showed that the overall adverse event profiles for patients treated with high or low dose lisinopril were similar in both nature and number. Predictable events resulting from ACE inhibition, such as hypotension or altered renal function, were manageable and rarely led to treatment withdrawal. Cough was less frequent in patients treated with high dose lisinopril compared with low dose.

In the GISSI-3 trial, which used a 2x2 factorial design to compare the effects of lisinopril and glyceryl trinitrate given alone or in combination for 6 weeks versus control in 19,394, patients who were administered the treatment within 24 hours of an acute myocardial infarction, lisinopril produced a statistically significant risk reduction in mortality of 11% versus control ($2p=0.03$). The risk reduction with glyceryl trinitrate was not significant but the combination of lisinopril and glyceryl trinitrate produced a significant risk reduction in mortality of 17% versus control ($2p=0.02$). In the sub-groups of elderly (age > 70 years) and females, pre-defined as patients at high risk of mortality, significant benefit was observed for a combined endpoint of mortality and cardiac function. The combined endpoint for all patients, as well as the high-risk sub-groups, at 6 months also showed significant benefit for those treated with lisinopril or lisinopril plus glyceryl trinitrate for 6 weeks, indicating a prevention effect for lisinopril. As would be expected from any vasodilator treatment, increased incidences of hypotension and renal dysfunction were associated with lisinopril treatment but these were not associated with a proportional increase in mortality.

In a double-blind, randomised, multicentre trial which compared lisinopril with a calcium channel blocker in 335 hypertensive Type 2 diabetes mellitus subjects with incipient nephropathy characterized by micro albuminuria, lisinopril 10mg to 20mg administered once daily for 12 months, reduced systolic/diastolic blood pressure by 13/10 mmHg and urinary albumin excretion rate by 40%. When compared with the calcium channel blocker, which produced a similar reduction in blood pressure, those treated with lisinopril showed a significantly greater reduction in urinary albumin excretion rate, providing evidence that the ACE inhibitory action of lisinopril reduced microalbuminuria by a direct mechanism on renal tissues in addition to its blood pressure lowering effect.

Lisinopril treatment does not affect glycaemic control as shown by a lack of significant effect on levels of glycated haemoglobin (HbA1c).

Renin-angiotensin system (RAS)-acting agents

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.

Paediatric population

In a clinical study involving 115 paediatric patients with hypertension, aged 6-16 years, patients who weighed less than 50 kg received either 0.625 mg, 2.5 mg or 20 mg of lisinopril once a day, and patients who weighed 50 kg or more received either 1.25 mg, 5 mg or 40 mg of lisinopril once a day. At the end of 2 weeks, lisinopril administered once daily lowered trough blood pressure in a dose-dependent manner with a consistent antihypertensive efficacy demonstrated at doses greater than 1.25 mg. This effect was confirmed in a withdrawal phase, where the diastolic pressure rose by about 9 mm Hg more in patients randomized to placebo than it did in patients who were randomized to remain on the middle and high doses of lisinopril. The dose-dependent antihypertensive effect of lisinopril was consistent across several demographic subgroups: age, Tanner stage, gender, and race.

5.2 Pharmacokinetic properties

Lisinopril is an orally active non-sulfydryl-containing ACE inhibitor.

Absorption

Following oral administration of lisinopril, peak serum concentrations occur within about 7 hours, although there was a trend to a small delay in time taken to reach peak serum concentrations in acute myocardial infarction patients. Based on urinary recovery, the mean extent of absorption of lisinopril is approximately 25% with inter-patient variability of 6-60% over the dose range studied (5-80mg).

The absolute bioavailability is reduced approximately 16% in patients with heart failure. Lisinopril absorption is not affected by the presence of food.

Distribution

Lisinopril does not appear to be bound to serum proteins other than to circulating angiotensin converting enzyme (ACE). Studies in rats indicate that lisinopril crosses the blood-brain barrier poorly.

Elimination

Lisinopril does not undergo metabolism and is excreted entirely unchanged into the urine. On multiple dosing lisinopril has an effective half-life of accumulation of 12.6 hours. The clearance of lisinopril in healthy subjects is approximately 50 ml/min. Declining serum concentrations exhibit a prolonged terminal phase, which does not contribute to drug accumulation. This terminal phase probably represents saturable binding to ACE and is not proportional to dose.

Hepatic impairment

Impairment of hepatic function in cirrhotic patients resulted in a decrease in lisinopril absorption (about 30% as determined by urinary recovery) but an increase in exposure (approximately 50%) compared to healthy subjects due to decreased clearance.

Renal impairment

Impaired renal function decreases elimination of lisinopril, which is excreted via the kidneys, but this decrease becomes clinically important only when the glomerular filtration rate is below 30ml/min. In mild to moderate renal impairment (creatinine clearance 30-80ml/min) mean AUC was increased by 13% only, while a 4.5-fold increase in mean AUC was observed in severe renal impairment (creatinine clearance 5-30 ml/min).

Lisinopril can be removed by dialysis. During 4 hours of haemodialysis, plasma lisinopril concentrations decreased on average by 60%, with a dialysis clearance between 40 and 55ml/min.

Heart failure

Patients with heart failure have a greater exposure of lisinopril when compared to healthy subjects (an increase in AUC on average of 125%), but based on the urinary recovery of lisinopril, there is reduced absorption of approximately 16% compared to healthy subjects.

Elderly

Elderly patients have higher blood levels and higher values for the area under the plasma concentration time curve (increased approximately 60%) compared with younger subjects.

Paediatric population

The pharmacokinetic profile of lisinopril was studied in 29 paediatric hypertensive patients, aged between 6 and 16 years, with a GFR above 30 ml/min/1.73m2. After doses of 0.1 to 0.2 mg/kg, steady state peak plasma concentrations of lisinopril occurredwithin 6 hours, and the extent of absorption based on urinary recovery was about 28%. These values are similar to those obtained previously in adults.

AUC and Cmax values in children in this study were consistent with those observed in adults.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. Angiotensin converting enzyme inhibitors, as a class, have been shown to induce adverse effects on the late foetal development, resulting in foetal death and congenital effects, in particular affecting the skull.

Foetotoxicity, intrauterine growth retardation and patent ductus arteriosus have also been reported.

These developmental anomalies are thought to be partly due to a direct action of ACE inhibitors on the foetal renin -angiotensin system and partly due to ischaemia resulting from maternal hypotension and decreases in foetal-placental blood flow and oxygen/nutrients delivery to the foetus.

6. Pharmaceutical particulars

6.1 List of excipients

Sr. No.	Material name	Specification	Remarks
1	Lactose monohydrate	BP	Diluents
2	Microcrystalline cellulose	BP	Diluents
3	Maize Starch	BP	Diluents
4	Povidone	BP	Binder
5	Isopropyl alcohol	BP	Solvent
6	Magnesium Stearate	BP	Lubricant
7	Purified Talc	BP	Glidant
8	Colloidal Anhydrous silica	BP	Glidant
9	Crosscarmellose sodium	BP	Disintegrant
10	Sodium lauryl sulphate	BP	Lubricant

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package. Keep container in the outer carton.

6.5 Nature and contents of container

14 tablets in Aluminium- PVC blister strip Pack. Such 2 blister strips are packed in a carton with an package insert.

6.6 Special precautions for disposal and other handling

Not applicable

7. Marketing Authorization Holder

SANGHARSH LIFECARE PVT LTD
A-502/503, Solitaire Corporate Park, Nr.Divya Bhaskar, S.G.Highway, Makarba, Ahmedabad- 380015

8. Marketing Authorization Number

9. Date of First Authorization /Renewal of the Authorization

10. Date of Revision of the Text