1.5.5 Clean Proposed Professional Information for Medicines for Human Use

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

SIMAYLA LISINOPRIL 5

SIMAYLA LISINOPRIL 10

SIMAYLA LISINOPRIL 20

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SIMAYLA LISINOPRIL 5

Each tablet contains lisinopril dehydrate equivalent to anhydrous lisinopril 5 mg

SIMAYLA LISINOPRIL 10

Each tablet contains lisinopril dihydrate equivalent to anhydrous lisinopril 10 mg

SIMAYLA LISINOPRIL 20

Each tablet contains lisinopril dihydrate equivalent to anhydrous lisinopril 20 mg

Contains sugar: mannitol.

Each 5 mg tablet contains 25 mg mannitol.

Each 10 mg tablet contains 50 mg mannitol.

Each 20 mg tablet contains 46 mg mannitol.

For full list if excipients, see section 6.1

3. PHARMACEUTICAL FORM

SIMAYLA LISINOPRIL 5: Light yellow coloured, uncoated, round tablets debossed with '5' on one side and scored on the other side.

SIMAYLA LISINOPRIL 10: Light yellow coloured, uncoated, round tablets debossed with '10' on one side and scored on the other side.

SIMAYLA LISINOPRIL 20: Light peach coloured, uncoated, round tablets debossed with '20' on one side and scored on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

SIMAYLA LISINOPRIL is indicated in the treatment of mild to moderate hypertension. It may be used alone or concomitantly with other classes of antihypertensive medicines.

SIMAYLA LISINOPRIL is indicated in the management of congestive heart failure as an adjunctive treatment with diuretics and, where appropriate, digoxin.

SIMAYLA LISINOPRIL is indicated for the treatment of haemodynamically stable patients, within 24 hours after acute myocardial infarction, to prevent the subsequent development of left ventricular dysfunction or heart failure and to improve survival. Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin and beta-blockers. Administration is by the oral route.

4.2 Posology and method of administration

Absorption of is not affected by food, and tablets may be administered before, during or after meals. **SIMAYLA LISINOPRIL** should be administered in a single dose. **SIMAYLA LISINOPRIL** should be taken at approximately the same time each day.

Mild to Moderate Hypertension

The recommended starting dose is 10 mg. The usual effective maintenance dosage is 20 mg administered in a single daily dose. Dosage should be adjusted according to blood pressure response.

A maximum dose of 40 mg a day in hypertension is recommended.

If the desired therapeutic effect cannot be achieved in a period of 2 to 4 weeks on a certain dose level, the dose can further be increased.

Diuretic-treated Patients

Symptomatic hypotension may occur following initiation of therapy with **SIMAYLA LISINOPRIL**; this is more likely in patients who are being treated concurrently with diuretics. Caution is recommended in all patients who may be volume- and/or salt-depleted. The diuretic should be discontinued 2 to 3 days before beginning therapy with **SIMAYLA LISINOPRIL** (see **Section 4.4**). In hypertensive patients in whom the diuretic cannot be discontinued, therapy with **SIMAYLA LISINOPRIL** should be initiated with a 5 mg dose. The subsequent dosage of **SIMAYLA LISINOPRIL** should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed.

Dosage Adjustment in Renal Impairment

A lower dose is required in the presence of renal impairment, in patients in whom diuretic therapy cannot be discontinued and in patients who are volume- and/or salt depleted for any reason. Dosage in patients with renal impairment should be based on creatinine clearance as outlined below:

Creatinine Clearance (ml/min)	**Initial Dose (mg/day)**
≤ 70 > 30	5 - 10

Safety has not been established in patients with creatinine clearance below 30 ml/min. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 20 mg daily.

Renovascular Hypertension

Special care is to be exercised in patients with renovascular hypertension because of the possibility of exaggerated response.

The dosage should be lowered to 2,5 mg or 5 mg and the patient should be monitored.

Congestive Heart Failure

In patients not adequately controlled by digoxin and/or diuretics, **SIMAYLA LISINOPRIL** may be added in a starting dose of 2,5 mg once a day. This may be increased at 4 week intervals in patients requiring an additional therapeutic effect. Dose adjustment should be based on the clinical response of the individual patients. The usual effective dosage range is 5 to 20 mg per day administered in a single daily dose.

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, prior to therapy with **SIMAYLA LISINOPRIL**. The effect of the starting dosage of **SIMAYLA LISINOPRIL** on blood pressure should be monitored carefully.

Acute Myocardial Infarction

Treatment with **SIMAYLA LISINOPRIL** may be started within 24 hours of the onset of symptoms. The first dose of **SIMAYLA LISINOPRIL** is 5 mg given orally, followed by 5 mg after 24 hours, 10 mg after 48 hours and then 10 mg once daily thereafter. Patients with a low systolic blood pressure (120 mmHg or less) should be given a lower dose, 2,5 mg orally (see **Section 4.4**). If hypotension occurs (systolic blood pressure less than or equal to 100 mmHg) a daily maintenance dose of 5 mg may be given with temporary reduction to 2,5 mg if needed. If prolonged hypotension occurs (systolic blood pressure less than 90 mmHg for more than 1 hour), **SIMAYLA LISINOPRIL** should be withdrawn.

Dosing should continue for 6 weeks. The benefit appears to be greatest in patients with large myocardial infarctions and evidence of impaired left ventricular function. Patients who develop symptoms of heart failure should continue with **SIMAYLA LISINOPRIL** (see **Congestive Heart Failure** above).

SIMAYLA LISINOPRIL is compatible with intravenous or transdermal glyceryl trinitrate.

Paediatric Use

Safety and effectiveness of **SIMAYLA LISINOPRIL** in children has not been established.

Use in the Elderly

There are no age-related changes in the efficacy or safety profile of **SIMAYLA LISINOPRIL**. When advanced age is associated with a decrease in renal function, however, the guidelines set out in the dose adjustment table (see **Renal Impairment** above) should be used to determine the starting dose of **SIMAYLA LISINOPRIL**. Thereafter, the dosage should be adjusted according to the blood pressure response.

4.3 Contraindications

- Hypersensitivity to lisinopril or any of the ingredients of **SIMAYLA LISINOPRIL**.
- A history of angioedema related to previous therapy with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines.
- Hereditary or idiopathic angioedema.
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Severe renal function impairment (creatinine clearance less than 30 ml/min).
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic stenosis.

- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see **Section 4.5**).
- Porphyria.
- Lithium therapy: Concomitant administration with **SIMAYLA LISINOPRIL** may lead to toxic blood concentrations of lithium (see **Section 4.5)**.
- Pregnancy and lactation (see **Section 4.4 and 4.6**).
- The concomitant use of **SIMAYLA LISINOPRIL** with aliskiren-containing products is contraindicated (see **Section 4.4 and 4.5**).
- Concomitant use of fluoroquinolones with ACE inhibitors/renin-angiotensin blockers is contraindicated in patients with moderate to severe renal impairment (see **Section 4.5).**

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving **SIMAYLA LISINOPRIL**, the treatment must be stopped promptly and switched to a different class of antihypertensive medicine. Should a woman contemplate pregnancy, the doctor should institute alternative medication (see **Section 4.3 and 4.6**).

ACE inhibitors can cause foetal and neonatal morbidity and mortality when administered to pregnant women.

ACE inhibitors pass through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms. Oligohydramnios, which may result in limb contractures, craniofacial deformities and hypoplastic lung development; as well as hypotension, renal failure, hyperkalaemia, oliguria and anuria in new-borns have been reported after administration of ACE inhibitors in the second and third trimesters. Cases

of detective skull ossification have been observed. Prematurity and low birth mass can occur.

The adverse effects to the embryo and foetus do not appear to have resulted from intra-uterine ACE inhibitor exposure limited to the first trimester.

Infants whose mothers may have taken **SIMAYLA LISINOPRIL** should be closely observed for hypotension, oliguria and hyperkalaemia.

Lisinopril crosses the human placenta. Limited experience indicates that peritoneal dialysis may be of some benefit in the clearance of lisinopril from the neonatal circulation. Lisinopril can theoretically be removed from the neonatal circulation by exchange transfusion.

Dual blockade of the rennin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers (ARBs) or aliskiren may increase the risk of hypotension, hyperkalaemia and decreases renal function (including acute renal failure). Dual blockade of RAAS through the combined use of **SIMAYLA LISINOPRIL** and aliskiren is therefore contraindicated (see **Section 4.3**).

Symptomatic Hypotension

Symptomatic hypotension may occur in uncomplicated hypertensive patients. In hypertensive patients receiving **SIMAYLA 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. In patients with congestive 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 these patients, initiation of therapy and dose adjustment should be monitored under close medical supervision.

In these patients, therapy should be started under medical supervision and the patients should be followed closely whenever the dose of **SIMAYLA LISINOPRIL** and/or diuretic is adjusted. Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contra-indication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with **SIMAYLA LISINOPRIL**.

If hypotension becomes symptomatic, a reduction of dose or discontinuation of **SIMAYLA LISINOPRIL** may be necessary.

Hypotension in Acute Myocardial Infarction

Treatment with **SIMAYLA 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 100 mmHg or lower or cardiogenic shock. During the first 3 days following the infarction, the dose should be reduced if the systolic blood pressure is 120 mmHg or lower. Maintenance doses should be reduced to 5 mg or temporarily to 2,5 mg if systolic blood pressure is 100 mgHg or lower. If hypotension persists (systolic blood pressure less than 90 mmHg for more than 1 hour) then **SIMAYLA LISINOPRIL** inhibitors, increases of blood urea and serum should be withdrawn.

Impaired Renal Function

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

In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with angiotensin converting enzyme inhibitors, increases of blood urea and serum creatinine, which is reversible upon discontinuation of therapy have been seen. This is especially likely in patients with renal insufficiency. Therefore **SIMAYLA LISINOPRIL** is contraindicated in these patients. Some hypertensive patients, with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine especially when **SIMAYLA LISINOPRIL** has been given concurrently with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of **SIMAYLA LISINOPRIL** and/or discontinuation of the diuretic and/or **SIMAYLA LISINOPRIL** may be required.

In acute myocardial infarction, treatment with **SIMAYLA 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 500 mg/24 hr. If renal dysfunction develops during treatment with **SIMAYLA LISINOPRIL** (serum creatinine concentration exceeding 265 micromol/l or a doubling from the pre-treatment value) then the doctor should consider withdrawal of **SIMAYLA LISINOPRIL**.

Haemodialysis Patients

Anaphylactoid reactions have been reported in patients undergoing certain haemodialysis procedures (e.g. with the high flux membrane AN 69) 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.

Hypersensitivity/Angioedema

Angioedema of the face, lips, tongue, glottis and/or larynx and extremities has been reported in patients treated with angiotensin converting enzyme inhibitors (including **SIMAYLA LISINOPRIL**). This may occur at any time during therapy. In such cases, **SIMAYLA LISINOPRIL** should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. In those cases where the swelling is confined to the face and lips, the condition may resolve without treatment, although anti-histamines may be useful in relieving symptoms. Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate emergency therapy should be administered promptly. This may include the administration of epinephrine (adrenaline) and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred. These patients should never receive any ACE-inhibitor again.

SIMAYLA LISINOPRIL causes 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**)

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 rechallenge.

Cough

Cough has been reported with the use of ACE-inhibitors such as **SIMAYLA LISINOPRIL**. Characteristically, the cough is non-productive, 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 medicines that produce hypotension, **SIMAYLA LISINOPRIL** may block the 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 - See **Section 4.5.**

Concomitant use of fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see **Section 4.3**). Renal function should be assessed before initiating treatment, and monitored during treatment, with fluoroquinolones or ACE inhibitors/renin-angiotensin receptor blockers.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

Rarely, patients receiving ACE inhibitors during low-density lipoproteins (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These

reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Hepatic failure

Very rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice 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.

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.

Mannitol

SIMAYLA LISINOPRIL contains mannitol and may have a laxative effect.

4.5 Interaction with other medicines and other forms of interaction

Dual blockade of the RAAS with ARBs, ACE inhibitors, or aliskiren

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 (see **Section 4.3 and 4.4**).
ACE inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

Diuretics

When a diuretic is added to the therapy of a patient receiving **SIMAYLA LISINOPRIL**, the antihypertensive effect is additive.

Patients already on diuretics and especially those, in whom diuretic therapy was recently instituted, may experience an excessive reduction of blood pressure when **SIMAYLA LISINOPRIL** is added. The possibility of symptomatic hypotension with **SIMAYLA LISINOPRIL** can be minimised by discontinuing the diuretic prior to initiation of treatment with **SIMAYLA LISINOPRIL**.

Other medicines

Indomethacin

Indomethacin may diminish the antihypertensive efficacy of concomitantly administered **SIMAYLA LISINOPRIL**. In some patients with compromised renal function who are being

treated with non-steroidal anti-inflammatory drugs (NSAIDS), the co-administration of **SIMAYLA LISINOPRIL** may result in further deterioration in renal function.

Nitrates

SIMAYLA LISINOPRIL has been used concomitantly with nitrates without evidence of clinically significant adverse interactions.

Lithium

Lithium elimination may be reduced by **SIMAYLA LISINOPRIL**. Therefore the concomitant use with **SIMAYLA LISINOPRIL** is contraindicated (see **Section 4.3**).

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.

Potassium supplements, potassium-sparing agents or potassium-containing salt substitutes:

Serum potassium tends to rise but usually remains within normal limits; however, hyperkalaemia may occur.

Risk factors for the development of hyperkalaemia include renal insufficiency, diabetes mellitus, and concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements or potassium-containing salt substitutes (see **Section 4.3**).

The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium.

If concomitant use of **SIMAYLA LISINOPRIL** and any of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium.

Fluoroquinolones

Concomitant use of fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers may precipitate acute kidney injury. See **Section 4.3**.

A case series of 16 reports of acute kidney injury (AKI) associated with enalapril and ciprofloxacin as co-suspect or interacting medicines was identified in VigiBase, the WHO global database of individual case safety reports. Analysis of 11 cases indicated that in most patients although clinical conditions and a number of medicines were likely to have increased their risk of AKI, including ACE inhibitor-related AKI, the event did not occur until after a ciprofloxacin prescription, lending weight to ciprofloxacin being the cause or a combined action of ciprofloxacin and enalapril. Furthermore, the interaction between ACE inhibitors and fluoroquinolones to precipitate acute kidney injury is a class effect for all ACE inhibitors and not just enalapril, and also a class effect of all the fluoroquinolones not just with ciprofloxacin. Thus, concomitant use of fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers may precipitate acute kidney injury. See **Section 4.3**.

Drugs that may increase the risk of angioedema

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) or tissue plasminogen activator may increase the risk of angioedema.

Non-steroidal anti-inflammatory medicinal products (NSAIDs) including acetylsalicylic acid ≥ 3 g/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.

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Antidiabetics

Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (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.

Co-trimoxazole (trimethoprim/sulfamethoxazole)

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

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

The use of **SIMAYLA LISINOPRIL** is contraindicated during pregnancy. Pregnant women should be informed of the potential hazards to the foetus and must not take **SIMAYLA LISINOPRIL** during pregnancy (see **Section 4.3**). Patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with **SIMAYLA LISINOPRIL** should be stopped immediately and if appropriate, alternative therapy should be started.

Foetal exposure to ACE inhibitors during the first trimester of pregnancy has been reported to be associated with an increased risk of malformations of the cardiovascular

(atrial and/or ventricular septal defect, pulmonic stenosis, patent ductus arteriosus) and central nervous system (spina bifida) and of kidney malformations.

SIMAYLA LISINOPRIL passes through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms.

Should exposure to **SIMAYLA LISINOPRIL** have occurred during the second or third trimesters of pregnancy, serial ultrasound examinations should be performed to assess the intra-amniotic environment. Patients and physicians should.be aware that oligohydrammos may not appear until after the foetus has sustained irreversible injury.

Oligohydramnios as well as hypotension, oliguria and anuria in new-borns, have been reported after administration of ***SIMAYLA LISINOPRIL*** *during the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur (see* ***Section 4.3 and 4.4****).*

4.7 Effects on ability to drive and use machines

When driving vehicles or operating machines, it should be taken into account that dizziness or tiredness may occur during treatment with **SIMAYLA LISINOPRIL**.

4.8 Undesirable effects

System Organ Class	**Frequent**	**Less frequent**	**Frequency Unknown**
Blood and the lymphatic system disorders		anaemia, haemolytic anaemia, neutropenia, decreases in haemoglobin, decreases in haematocrit, thrombocytopenia, agranulocytosis, bone marrow depression, leucopenia, lymphadenopathy, autoimmune diseases.	

Immune system disorders		anaphylactoid reactions, angioedema	
Endocrine disorders		syndrome of inappropriate antidiuretic hormone secretion (SIADH)	
Metabolism and nutrition disorders		hypoglycaemia	
Psychiatric disorders		mood alterations, mental confusion	depressive symptoms
Nervous system disorders	headache, dizziness	paraesthesia, vertigo, taste disturbance, sleep disturbances, olfactory disturbance	syncope
Cardiac disorders	orthostatic effects (including hypotension)	myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients, chest pain, palpitations, tachycardia	
Vascular disorders		Raynaud's phenomenon	
Respiratory, thoracic and mediastinal disorders	cough	rhinitis, bronchospasm, sinusitis, allergic alveolitis/eosinophilic pneumonia	
Gastrointestinal disorders	diarrhoea, vomiting	nausea, abdominal pain, indigestion, dry mouth, pancreatitis, intestinal angioedema, stomatitis	
Hepatobiliary disorders[1]		hepatitis – either hepatocellular or	

		cholestatic, jaundice and hepatic failure	
Skin and subcutaneous tissue disorders[2]		rash, pruritus, urticaria, alopecia, psoriasis, hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx, sweating, pemphigus, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, cutaneous pseudolymphoma, diaphoresis	
Musculoskeletal and connective tissue disorders		muscle cramps	
Renal and urinary disorders	renal dysfunction	uraemia, acute renal failure, oliguria/anuria	
Reproductive system and breast disorders		impotence, gynaecomastia	
General disorders and administration site conditions		asthenia, fatigue	
Investigations		increases in blood urea, increases in serum creatinine, increases in liver enzymes, hyperkalaemia, increases	

		in serum bilirubin, hyponatraemia, decrease in haemoglobin	

1 – Very rarely, it has been reported that in some patients the undesirable development of hepatitis has progressed to hepatic failure. Patients receiving **SIMAYLA LISINOPRIL** who develop jaundice or marked elevation of hepatic enzymes should discontinue **SIMAYLA LISINOPRIL** and receive appropriate medical follow up.

2 - A symptom complex has been reported which may include some or all of the following: fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, a positive anti-nuclear antibody (ANA), elevated erythrocyte sedimentation rate (ESR), eosinophilia, and leucocytosis, rash, photosensitivity or other dermatologic manifestations may occur

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

The symptoms of overdosage may include severe hypotension, circulatory shock, electrolyte disturbances hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough renal failure. Treatment is symptomatic and supportive. 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 sulphate). 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

A7.1.3 Other hypotensives.

Pharmacotherapeutic group: Angiotensin-converting enzyme inhibitors, ATC code: C09A A03

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.

While the mechanism through which lisinopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, lisinopril is also antihypertensive 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.

In patients with diabetes mellitus who have microalbuminuria,, lisinopril reduces the urinary albumin excretion.

5.2 Pharmacokinetic properties

<u>Absorption:</u>

Following oral administration, peak serum concentrations occur within 6 to 8 hours, although there is a trend to a small delay in time taken to reach peak plasma concentrations in acute myocardial infarction patients. The extent of absorption of lisinopril is approximately 25 %, with interpatient variability (6-60 %) at all doses tested (5-80 mg). 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).

Elimination:

Lisinopril is excreted unchanged in the urine. The clearance of lisinopril In healthy subjects is approximately 50 ml/min. Upon multiple dosing, lisinopril exhibits an effective half-life of accumulation of 12,6 hours. Declining serum concentrations exhibits 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 30 ml/min.

Pharmacokinetic parameters of Lisinopril to different groups of renal patients after administration of a multiple 5 mg dose

Renal function measured by creatinine clearance	**n**	**Cmax (ng/ml)**	**Tmax (hr)**	**AUC (0-24 hrs) (ng/hr/ml)**	**$T_{½}$ (hr)**
> 80 ml/min	6	40,3	6	492 ± 172	6,0± 1,1
30-80 ml/min	6	36,6	8	555 ± 364	11,8 ± 1,9
5-30 ml/min	6	106,7	8	2228 ± 938	19,5 ± 5,2

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 55 ml/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:

Older patients have higher blood levels and higher values for the area under the plasma concentration time curve (increased approximately %) than younger patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous calcium hydrogen phosphate, ferric oxide, magnesium stearate, maize starch, mannitol and pregelatinised starch maize.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store at or below 25 °C, protected from light and moisture.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

SIMAYLA LISINOPRIL 5:

Carton containing three PVdC-coated PVC blister strips of 10 tablets each.

SIMAYLA LISINOPRIL 10:

Carton containing three PVdC- coated PVC blister strips of 10 tablets each.

SIMAYLA LISINOPRIL 20:

Carton containing three PVdC- coated PVC blister strips of 10 tablets each.

6.6 Special precautions for disposal and other handling

Return all unused or expired medicines to your pharmacist for safe disposal. Do not dispose of unused medicines in drains or sewerage systems (e.g. toilets).

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road

Stormill Ext. 1

Roodepoort

1724

South Africa

8. REGISTRATION NUMBERS

SIMAYLA LISINOPRIL 5: 36/7.1.3/0112

SIMAYLA LISINOPRIL 10: 36/7.1.3/0113

SIMAYLA LISINOPRIL 20: 36/7.1.3/0114

Namibia only:

SIMAYLA LISINOPRIL 5: NS2 Reg No.: 08/7.1.3/0042

SIMAYLA LISINOPRIL 10: NS2 Reg No.: 08/7.1.3/0043

SIMAYLA LISINOPRIL 20: NS2 Reg No.: 08/7.1.3/0021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of registration: April 2003

10. DATE OF REVISION OF THE TEXT

24 January 2022