LISO 2,5/5/10/20

PROPOSED PROFESSIONAL INFORMATION FOR

LISO

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

LISO 2,5 tablets

LISO 5 tablets

LISO 10 tablets

LISO 20 tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LISO 2,5: Each tablet contains lisinopril dihydrate equivalent to 2,5 mg lisinopril.

LISO 5: Each tablet contains lisinopril dihydrate equivalent to 5,0 mg lisinopril.

LISO 10: Each tablet contains lisinopril dihydrate equivalent to 10,0 mg lisinopril.

LISO 20: Each tablet contains lisinopril dihydrate equivalent to 20,0 mg lisinopril.

LISO contains sugar (mannitol) in the following quantities; LISO 2,5 and LISO 5 (44,00 mg), LISO 10 and LISO 20 (88,00 mg).

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

LISO 2,5: White to off-white coloured, round, biconvex, uncoated tablets with breakline on one side and “2.5” on other side.

LISO 5: Pink coloured, round, biconvex, uncoated tablets with breakline on one side and “5” on other side.

LISO 10: Pink coloured, round, biconvex, uncoated tablets with breakline on one side and “10” on other side.

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LISO 20: Pink coloured, round, biconvex, uncoated tablets with breakline on one side and “20” on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension:

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

Congestive heart failure:

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

Acute myocardial infarction:

LISO 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

LISO should be administered in a single daily dose preferably at the same time every day. Absorption of **LISO** is not affected by food, and **LISO** can be taken with or without food. Dosage should be adjusted according to blood pressure response.

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. 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 **LISO**; this is more likely in patients who are being treated currently 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 **LISO** (see **WARNINGS AND SPECIAL PRECAUTIONS**). In hypertensive patients in whom the diuretic cannot be discontinued, therapy with **LISO** should be initiated with a 5 mg dose. The subsequent dosage of **LISO** should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed.

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Dosage adjustment in renal impairment:

A lower dose is required in the presence of mild to moderate 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 mild to moderate renal impairment should be based on creatinine clearance as outlined below:

Creatinine clearance (ml/min)	Starting dose (mg/day)
31 - 80	5 - 10

The dosage may be titrated upward until blood pressure is controlled or to a maximum of 20 mg daily.

Safety has not been established in patients with creatinine clearance below 30 ml/min (see **CONTRAINDICATIONS**).

LISO is contraindicated in severe renal impairment.

Renovascular hypertension:

Special care to be exercised in some 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, **LISO** may be added in a starting dose of 2,5 mg once a day. Dose adjustment should be based on the clinical response of the individual patients.

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The dose of **LISO** should be increased:

- by increments of no greater than 10 mg
- at intervals of no less than 2 weeks
- to the highest dose tolerated by the patient up to a maximum of 35 mg once daily.

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 **LISO**. The effect of the starting dosage of **LISO** on blood pressure should be monitored carefully.

Acute myocardial infarction:

Treatment with **LISO** may be started within 24 hours of the onset of symptoms.

The first dose of **LISO** 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) when treatment is started or during the first 3 days after the infarct should be given a lower dose - 2,5 mg orally (see **WARNINGS AND SPECIAL PRECAUTIONS**).

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 reductions to 2,5 mg if needed. If prolonged hypotension occurs (systolic blood pressure less than 90 mm Hg for more than 1 hour), **LISO** 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 **LISO** (see **DOSAGE AND DIRECTIONS FOR USE** for congestive heart failure).

LISO is compatible with intravenous or transdermal glyceryl trinitrate.

Paediatric use:

Safety and effectiveness of **LISO** in children have not been established.

Use in the elderly:

There are no age-related changes in the efficacy or safety profile of **LISO**. 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 **LISO**. Thereafter, the dosage should be adjusted according to the blood pressure response.

4.3 Contraindications

- Hypersensitivity to lisinopril or any ingredients of **LISO**
- Concomitant use of fluoroquinolones with Angiotensin Converting Enzyme (ACE) inhibitors, such as **LISO**, is contraindicated in patients with moderate to severe renal impairment (creatinine clearance ≤ 30 ml/min) and in elderly patents
- A history of angioedema related to previous therapy with 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 **INTERACTIONS**)
- Porphyria

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- Lithium therapy: Concomitant administration with **LISO** may lead to toxic blood concentrations of lithium (see **INTERACTIONS** and **WARNINGS AND SPECIAL PRECAUTIONS**)
- Pregnancy and lactation (see **HUMAN REPRODUCTION**)
- The concomitant use of **LISO** with renin inhibitors is contraindicated (see **WARNINGS AND SPECIAL PRECAUTIONS** and **INTERACTIONS**)

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving **LISO**, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see **CONTRAINDICATIONS** and **HUMAN REPRODUCTION**).

Fluoroquinolones:

Concomitant use of fluoroquinolones with Angiotensin Converting Enzyme (ACE) inhibitors, such as **LISO**, may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and in elderly patients (see **CONTRAINDICATIONS**).

Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or ACE inhibitors whether used separately or concomitantly.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)*:*

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

LISO should not be used concomitantly with renin inhibitors (see **CONTRAINDICATIONS**).

LISO should be used with caution in the following conditions:

Hypersensitivity/angioedema:

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients using **LISO**. This may occur at any time during therapy.

In such cases, **LISO** should be discontinued promptly and appropriate treatment and monitoring should be instituted to ensure complete resolution of symptoms prior to discharging the patient. 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. 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 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 (see **CONTRAINDICATIONS**).

LISO 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 **CONTRAINDICATIONS**).

Renal function impairment:

In patients with congestive heart failure, hypotension following the initiation of therapy with **LISO** 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 of a solitary kidney, who have been treated with ACE-inhibitors, increases of blood urea and serum creatinine,

reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency.

Increases in blood urea and serum creatinine have developed in some hypotensive patients with no apparent pre-existing renal vascular disease, especially when **LISO** has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of **LISO** and/or discontinuation of the diuretic and/or **LISO** may be required.

In acute myocardial infarction, treatment with **LISO** should not be initiated in patients with evidence of renal dysfunction (serum creatinine concentrations exceeding 177 micromol/l and/or proteinuria exceeding 500 mg/24 hours). If renal dysfunction develops during treatment with **LISO** (serum creatinine concentrations exceeding 265 micromol/l or doubling of the pre-treatment value) then **LISO** may need to be withdrawn (see **CONTRAINDICATIONS**).

LISO should not be used in patients with renovascular disease or suspected renovascular disease but it may be used cautiously in severe resistant hypertension in such patients. In this instance **LISO** should only be used under specialist supervision. The elderly, patients with peripheral vascular diseases or generalised atherosclerosis may be at high risk because they have asymptomatic renovascular disease (see **DOSAGE AND DIRECTIONS FOR USE**).

Symptomatic hypotension:

Symptomatic hypotension may occur in uncomplicated hypertensive patients. In hypertensive patients receiving **LISO**, 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.

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Myocardial infarction and cerebrovascular accidents could result due to an excessive fall in blood pressure in high-risk patients e.g. those with ischaemic heart or cerebrovascular disease. If hypotension occurs, the patient should be placed in the supine position and if necessary 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 congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with **LISO**. This effect is anticipated and is not usually a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of **LISO** may be necessary.

Hypotension in acute myocardial infarction:

Treatment with **LISO** must not be initiated in acute myocardial infarction patients who are at risk of further serious haemodynamic deterioration after treatment with a vasodilator. These include 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 mmHg or lower. If hypotension persists (systolic blood pressure less than 90 mmHg for more than 1 hour) then **LISO** should be withdrawn.

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Surgery or anaesthesia:

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

Diabetic patients:

In diabetic patients treated with oral antidiabetic medicines or insulin, glycaemic control should be closely monitored during the first month of treatment with **LISO**.

Anaphylactoid reactions in haemodialysis patients:

Anaphylactoid reactions have been reported in patients undergoing certain haemodialysis procedures (e.g. with the high flux membrane AN 69 and during low-density lipoproteins (LDL) apheresis with dextran sulphate) 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 medicine.

Desensitisation:

Anaphylactoid reactions have occurred in patients using **LISO** during desensitising protocols involving for example, hymenoptera venom. In the same patients, these reactions were avoided when **LISO** was temporarily withheld but they reappeared upon inadvertent rechallenge.

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Cough:

Cough has been reported with the use of **LISO**. 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.

Autoimmune disease:

Autoimmune disease, especially systemic lupus erythematosus, other collagen vascular diseases or scleroderma increase the risk for patients to develop neutropenia or agranulocytosis, especially when they also have impaired renal function.

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 may occur. Neutropenia and agranulocytosis are reversible after discontinuation of the ACE-inhibitor. **LISO** 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 **LISO** 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.

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Aortic and mitral valve stenosis / hypertrophic cardiomyopathy:

LISO 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.

Hepatic failure:

ACE-inhibitors have been very rarely 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 taking **LISO** who develop jaundice or marked elevations of hepatic enzymes should discontinue taking **LISO** and receive appropriate medical follow-up.

Hyperkalaemia:

Elevations in serum potassium have been observed in some patients treated with **LISO**. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, diabetes mellitus, or those using concomitant potassium-sparing diuretics (e.g spironolactone, triamterene or amiloride), potassium supplements or potassium-containing salt substitutes, or those patients taking other medicines associated with increases in serum potassium (e.g. heparin, the combination trimethoprim/sulphamethoxazole also known as co-trimoxazole). If concomitant use of the above-mentioned medicines is deemed appropriate, regular monitoring of serum potassium is recommended.

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Lithium:

The combination of lithium and **LISO** is generally not recommended (see **INTERACTIONS** and **CONTRAINDICATIONS**).

4.5 Interaction with other medicines and other forms of interaction

Fluoroquinolones:

Concomitant use of fluoroquinolones and Angiotensin Converting Enzyme (ACE) inhibitors, such as **LISO**, may precipitate acute kidney injury.

The mechanism of the possible interaction between the different classes of medicines, over and above the different mechanisms of kidney damage, is unknown (see **CONTRAINDICATIONS**).

Dual blockade of the RAAS with ARBs, ACE-inhibitors or renin inhibitors:

Clinical data has shown that the dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or renin inhibitors is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (see **CONTRAINDICATIONS** and **WARNINGS AND SPECIAL PRECAUTIONS**).

Lithium:

Concomitant use of **LISO** with lithium is contraindicated.

Lithium elimination may be reduced and this may lead to toxicity (see **CONTRAINDICATIONS** and **WARNINGS AND SPECIAL PRECAUTIONS**).

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Potassium supplements, potassium-sparing medicines 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. 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 (see **CONTRAINDICATIONS**).

Diuretics:

When a diuretic is added to the therapy of a patient receiving **LISO**, 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 **LISO** is added. The possibility of symptomatic hypotension with **LISO** can be minimised by discontinuing the diuretic prior to initiation of treatment with **LISO**.

Antidiabetics:

Concomitant administration of **LISO** and antidiabetic medicines (insulins, oral hypoglycaemic medicines) may cause an increased blood glucose lowering effect with risk of hypoglycaemia. This phenomenon appears to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Non-steroidal anti-inflammatory drugs (NSAIDs including aspirin ≥ 3 g/day):

NSAIDs reduce the antihypertensive effects of **LISO**. In some patients with compromised renal function who are being treated with NSAIDs, the co-administration of **LISO** may result in further deterioration in renal function. In elderly patients, the combination of **LISO** with NSAIDs should

be administered with caution. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy and thereafter periodically.

Nitrates:

LISO has been used concomitantly with nitrates and an additive fall in blood pressure may occur.

Alcohol and hypotension-producing medicines:

The antihypertensive effect is additive.

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 **LISO**.

Tricyclic antidepressants / antipsychotics / anaesthetics:

Concomitant use of certain anaesthetic medicines, tricyclic antidepressants and antipsychotics with **LISO** may result in further reduction of blood pressure.

Sympathomimetics:

Sympathomimetics may reduce the antihypertensive effects of **LISO**.

Tissue plasminogen activators:

Concomitant treatment with tissue plasminogen activators may increase the risk of angioedema.

Information on excipients of LISO:

Contains mannitol and may have a laxative effect.

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4.6 Fertility, pregnancy and lactation

The use of **LISO** is contraindicated during pregnancy. Pregnant women should be informed of the potential hazards to the foetus and must not take **LISO** during pregnancy (see **CONTRAINDICATIONS**). 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 **LISO** 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 (microcephaly spina bifida) and of kidney malformations.

LISO passes through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms. Oligohydramnios as well as hypotension, oliguria and anuria in new-borns, have been reported after administration of **LISO** during the second and third trimester. Cases of defective skull ossification have been observed.

Prematurity and low birth mass can occur (see **CONTRAINDICATIONS**).

Safety in lactation has not been established.

4.7 Effects on the ability to drive and use machines

Caution should be advised when driving or performing tasks requiring alertness because **LISO** may cause dizziness.

4.8 Undesirable effects

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system	*Less frequent*	Bone marrow depression, anaemia, thrombocytopenia, agranulocytosis, haemolytic anaemia, leucopenia,

disorders		neutropenia, lymphadenopathy, haemoglobin decreased, haemocrit decreased
Immune system disorders	*Less frequent*	Autoimmune disease, hypersensitivity/angioedema reactions: angioedema of the face, which may be fatal, extremities, lips, tongue, glottis and/or larynx and intestinal angioedema
Endocrine disorders	*Less frequent*	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders	*Less frequent*	Hyperkalaemia, hyponatraemia, hypoglycaemia
Psychiatric disorders	*Less frequent*	Mood alterations, mental confusion, depressive symptoms
Nervous system disorders	*Frequent* *Less frequent*	Dizziness, headache Paraesthesia, vertigo, sleep disturbances, hallucinations, syncope, olfactory disturbances
Cardiac disorders	*Less frequent*	Orthostatic effects (including myocardial infarction, cerebrovascular accident, palpitations, tachycardia), possibly secondary to excessive hypotension in high risk patients
Vascular disorders	*Less frequent*	Hypotension, Raynaud's phenomenon, orthostatic effects
Respiratory, thoracic and mediastinal disorders	*Frequent* *Less frequent*	Cough Bronchospasm, rhinitis, sinusitis, allergic alveolitis, eosinophilic pneumonia
Gastrointestinal	*Frequent*	Diarrhoea, vomiting

disorders	*Less frequent*	Nausea, abdominal pain, indigestion, dry mouth, pancreatitis, taste disturbances
Hepatobiliary disorders	*Less frequent*	Hepatitis (hepatocellular or cholestatic), jaundice, increased liver enzymes, increased serum bilirubin, increased hepatic failure
Skin and subcutaneous tissue disorders	*Less frequent*	Rash, urticaria, diaphoresis, alopecia, pruritus, psoriasis, sweating, cutaneous pseudolymphoma, severe skin disorders including pemphigus, toxic epidermal necrolysis, Stevens Johnson Syndrome, erythema multiforme
Renal and urinary disorders	*Less frequent*	Uraemia, oliguria, anuria, renal dysfunction, acute renal failure, increased serum creatinine
Reproductive system and breast disorders	*Less frequent*	Impotence, gynaecomastia
General disorders and administrative site conditions	*Less frequent*	Fatigue, asthenia, a symptom complex which may include: fever, vasculitis, myalgia, arthritis/arthralgia, a positive antinuclear antibodies (ANA), elevated erythrocyte sedimentation rate, eosinophilia and leucocytosis. Rash, photosensitivity, other dermatological manifestations

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of BETAHISTINE 24 UNICORN is important. It allows continued monitoring of the benefit/risk balance of BETAHISTINE 24 UNICORN. Health care providers are asked to report any suspected adverse reactions via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

Report all side effects to Unicorn Pharmaceuticals (Pty) Ltd to enquiries@unicornpharma.co.za

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By reporting side effects, you can help provide more information on the safety of LISO.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

Category and class: A 7.1.3 Other hypotensives.

5.1 Pharmacodynamic properties

Pharmacodynamic properties:

Lisinopril is an orally active ACE-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:

Absorption:

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Following oral administration of lisinopril, peak serum concentrations occur within about 7 hours, although there is a trend to a small delay in time taken to reach peak plasma concentrations in acute myocardial infarction patients. Based on urinary recovery, about 25 % of a dose is absorbed on average, but the absorption varies considerably between individuals, ranging from about 6 to 60 % over a dose range of 5 – 80 mg.

In patients with heart failure the absolute bioavailability is reduced by approximately 16 %.

Lisinopril absorption is not affected by the presence of food.

Elimination:

Lisinopril is excreted unchanged in the urine. The clearance of lisinopril in healthy patients is approximately 50 ml/min. The effective half-life for accumulation after multiple doses is 12,6 hours.

Declining serum concentrations exhibit a prolonged terminal phase which does not contribute to lisinopril accumulation. This terminal phase probably represents saturable binding to ACE and is not proportional to dose.

Hepatic impairment:

A decrease in lisinopril absorption (about 30 % as determined by urinary recovery) occurs as a result of hepatic function impairment in cirrhotic patients. However an approximate 50 % increase in exposure results, compared to healthy patients, due to decreased clearance.

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Renal impairment:

Impaired renal function decreases elimination of lisinopril, which is excreted via the kidneys. This decrease only becomes clinically important when the glomerular filtration rate is below 30 ml/min.

Lisinopril is removed by haemodialysis.

During 4 hours of haemodialysis, plasma lisinopril concentrations decrease 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 patients (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 patients.

Elderly:

Older patients have higher blood levels and higher values for the area under the plasma concentration time curve (an increase of approximately 60 %) compared with younger patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inactive ingredients:

Calcium hydrogen phosphate dihydrate, colloidal silica anhydrous, mannitol, magnesium stearate, maize starch, red iron oxide (excluding 2,5 mg tablet), starch pre-gelatinised.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

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

Keep the blisters in the carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

LISO tablets are packed in clear transparent PVC/PVDC and silver aluminium blister strips containing 10 tablets. Three blister strips are packed in an outer carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Unicorn Pharmaceuticals (Pty) Ltd

Corner Searle and Pontac Streets

Cape Town

South Africa

8001

8. REGISTRATION NUMBER

LISO 2,5: A43/7.1.3/0662

LISO 5: A43/7.1.3/0663

LISO 10: A43/7.1.3/0664

LISO 20: A43/7.1.3/0665

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 11 June 2018

10. DATE OF REVISION OF THE TEXT

Date of latest approval: 30 September 2019