APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S3

PROPRIETARY NAME (and dosage form):

LIRACEN 1,25 mg (Capsule)

LIRACEN 2,5 mg (Capsule)

LIRACEN 5 mg (Capsule)

LIRACEN 10 mg (Capsule)

COMPOSITION:

LIRACEN 1,25 mg:

Each hard gelatin capsule contains ramipril 1,25 mg. Sugar free.

LIRACEN 2,5 mg:

Each hard gelatin capsule contains ramipril 2,5 mg. Sugar free.

LIRACEN 5 mg:

Each hard gelatin capsule contains ramipril 5 mg. Sugar free.

LIRACEN 10 mg:

Each hard gelatin capsule contains ramipril 10 mg. Sugar free.

The other ingredients of **LIRACEN** are silica hydrophobic colloidal anhydrous and starch pregelatinised. The capsule shells contain gelatin, iron oxide yellow (C.I. No: 77492), sodium lauryl sulphate, titanium dioxide (C.I. No: 77891) and water. **LIRACEN 2,5 mg** shells contain ponceau 4R (C.I. No.: 16255). **LIRACEN 5 mg** and **LIRACEN 10 mg** contain patent blue V (C.I. No.: 42051) and ponceau 4R (C.I. No.: 16255). The black ink contains black iron oxide (C.I. No: 77499), butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol, shellac and strong ammonia solution.

PHARMACOLOGICAL CLASSIFICATION:

A 7.1.3 Other hypotensives.

PHARMACOLOGICAL ACTION

Pharmacodynamics:

Ramipril is a long-acting angiotensin converting enzyme (ACE) inhibitor. Ramipril is a prodrug. After absorption from the gastro-intestinal tract, ramipril is hydrolysed in the liver to form the active angiotensin converting enzyme inhibitor, ramiprilat. Ramipril increases plasma renin activity and decreases plasma concentrations of angiotensin II and aldosterone.

ACE inhibition causes the beneficial haemodynamic effects and the consequent reduction in angiotensin II results in dilation of peripheral vessels and reduction in vascular resistance. Ramipril binds to angiotensin converting enzyme at both tissue and plasma levels.

Angiotensin converting enzyme is identical to kininase II, one of the enzymes responsible for the degradation of bradykinin. There is evidence that ACE inhibition by ramipril appears to have some effects on the kallikrein-kinin-prostaglandin systems. It is assumed that these mechanisms also contribute to the hypotensive activity of ramipril, and may be at least co-responsible for certain adverse reactions, e.g. dry cough.

In patients with non-diabetic or diabetic overt nephropathy, the mode of action (pharmacodynamics) is that ramipril decreases the rate of progression of renal insufficiency. In patients with diabetic nephropathy and hypertension, ramipril reduces albumin excretion and the decline in glomerular filtration rate.

Pharmacokinetics:

Following oral administration, ramipril is absorbed from the gastro-intestinal tract and peak plasma concentrations of ramipril are reached within one hour. Ramipril is a prodrug. Ramipril is converted in the liver to its diacid metabolite, ramiprilat, by cleavage of an ester group. Peak plasma concentrations of ramiprilat are reached two to four hours after medicine intake of ramipril. The extent of absorption is estimated to be 30 % to 60 %, based on the urinary recovery of ramipril and its metabolites.

Food intake has no relevant influence on the extent of absorption, but the rate is reduced by food.

The protein binding of ramipril is about 73 % and that of ramiprilat about 56 %.

Ramipril is almost completely metabolised and the metabolites are excreted mainly via the kidneys. Beside the bioactive metabolite ramiprilat, further inactive metabolites have been identified, i.e. diketopiperazine ester, diketopiperazine acid, and conjugates.

Plasma concentrations of ramiprilat decline in a polyphasic manner. After multiple once daily administration of ramipril, the effective half-life of ramiprilat is 13 to 17 hours for 5 to 10 mg ramipril and several times longer for lower doses such as 1,25 mg to 2,5 mg ramipril.

The prolonged half-life at low dosages is due to a high fraction of the metabolite being bound to the angiotensin converting enzyme at low plasma concentrations and thus a slow dissociation of this enzyme inhibitor complex. However, a shorter half-life with high dosages is observed, due to a higher free fraction, leading to easier dissociation.

Steady-state plasma concentrations of ramiprilat, after once daily dosing of the usual doses of ramipril, are reached at about treatment day four.

Patients with renal impairment:

In patients with impaired renal function, the elimination of ramipril and ramiprilat from plasma is delayed and the urinary excretion reduced.

INDICATIONS

LIRACEN are indicated for:

- Mild to moderate hypertension.
- Cardiac failure following myocardial infarction.
- To reduce proteinuria and the decline in glomerular filtration rate in patients with diabetic nephropathy and hypertension.
- To reduce the risk of myocardial infarction, stroke or cardiovascular death and to reduce the need for revascularisation procedures in patients with an increased cardiovascular risk [such as manifest coronary heart disease (with or without a history of myocardial infarction), a history of stroke or a history of peripheral vascular disease.]
- To reduce the risk of myocardial infarction, stroke or cardiovascular death in diabetic patients.

CONTRA-INDICATIONS

- Sensitivity to ramipril or any of the components of **LIRACEN**.
- 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.
- Porphyria.
- Lithium therapy: Concomitant administration with **LIRACEN** may lead to toxic blood concentrations of lithium.
- Pregnancy and lactation (see **"PREGNANCY AND LACTATION"**).
- **LIRACEN** is not recommended for use in children.

WARNINGS AND SPECIAL PRECAUTIONS

Should a woman become pregnant while receiving LIRACEN, the treatment must be stopped promptly and switched to a different class of antihypertensive medicine (See "PREGNANCY AND LACTATION"). Should a woman contemplate pregnancy, the doctor should consider alternate medication. (See "CONTRA-INDICATIONS" and "PREGNANCY AND LACTATION").

LIRACEN should be given with caution in the following conditions:

- Cerebrovascular disease or ischaemic heart disease – Reduction in blood pressure could aggravate these conditions and may result in cerebrovascular accidents and myocardial infarction.
- Volume depleted patients (e.g. by dietary salt restriction, by diuretic therapy, diarrhoea, vomiting or dialysis) – Although it may occur in normo volumic patients, hypotension is more likely to occur in volume depleted patients. A sudden reduction in angiotensin II may result in severe and sudden hypotension. Treatment with **LIRACEN** for these products should be initiated under close medical supervision, starting with a low dose. The patient should be in a recumbent position to minimize this effect. If necessary, an intravenous infusion of 0,9 %

sodium chloride (NaCl) may be administered. There is also an increased risk of **LIRACEN** induced renal failure, especially in those with congestive heart failure.

- Patients at a high risk of symptomatic hypotension e.g. patients with volume or salt depletion with or without hyponatremia should have these conditions corrected before therapy with **LIRACEN**. Monitoring is required after initiating therapy.
- Autoimmune disease, especially systemic lupus erythematosus, other collagen vascular disease or scleroderma or in patients also given immunosuppressive therapy increases the risk for development of agranulocytosis or neutropenia. Regular white blood cell counts may be necessary.
- In acute myocardial infarction, patients may develop persistent hypotension and/or impaired renal function.
- In acute myocardial infarction, treatment with **LIRACEN** should not be initiated in patients with evidence of renal dysfunction (serum creatinine concentrations exceeding 177 µmol/l or proteinuria exceeding 500 mg/24 hours). If renal dysfunction develops during treatment (serum creatinine concentrations exceeding 177 µmol/l or doubling of the pre-treatment value) then **LIRACEN** may need to be withdrawn (see **"CONTRA-INDICATIONS"**).
- Hypotension in acute myocardial infarction – Treatment with **LIRACEN** 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 a systolic blood pressure of 99,98 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 119,93 mmHg or lower. Maintenance doses should be reduced if systolic blood pressure is 99,98 mmHg or lower. **LIRACEN** should be withdrawn if hypotension persists (systolic blood pressure less than 89,93 mmHg for more than 1 hour).
- Bone marrow depression – Increased risk of agranulocytosis and neutropenia.
- Diabetes mellitus – Increased risk of hyperkalaemia, as well as hypoglycaemia may occur.
- Hyperkalaemia – **LIRACEN** may cause an increase in serum potassium levels.
- Renovascular disease – **LIRACEN** 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, **LIRACEN** must only be used under the supervision of a specialist. Patients with peripheral vascular diseases or generalised atherosclerosis and the elderly may have asymptomatic renovascular disease (see **"DOSAGE AND DIRECTIONS FOR USE"**).

- Renal artery stenosis, bilateral or in one kidney or renal transplant **–** Increased risk of renal function impairment may increase in blood urea and serum creatinine concentrations, which may be reversible upon discontinuation of therapy.
- Renal function impairment – Decreased elimination of **LIRACEN** resulting in an increased risk of hyperkalaemia. These patients may require lower doses of **LIRACEN**.
- Anaphylactoid reactions have occurred in patients using ACE inhibitors during desensitising protocols involving for example, hymenoptera venom.
- Anaphylactoid reactions have been reported in patients exposed to either high-flux membrane dialysis or low-density lipoprotein apheresis with dextran sulphate absorption.
- Hypersensitivity/angioedema – If angioedema of the extremities, face, lips, tongue, glottis and/or larynx is observed in patients treated with **LIRACEN**, then **LIRACEN** should be promptly discontinued. These patients should be monitored to ensure complete resolution of symptoms (see **"CONTRA-INDICATIONS"**).
- 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. This may include the administration of epinephrine and/or the maintenance of a patent airway. Until complete and sustained resolution of symptoms has occurred, the patient should be under close medical supervision. **These patients should never receive LIRACEN again.**
- **LIRACEN** causes a higher rate of angioedema in black patients than in non-black patients.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, and amiloride may lead to hyperkalaemia which may be severe and lead to cardiac conduction abnormalities, dysarrythmias and cardiac arrest (see **"CONTRA-INDICATIONS"**).
- The metabolism of the parent compound ramipril and therefore the formation of the bioactive metabolite ramiprilat is decelerated in patients with impaired liver function. This results in

markedly elevated plasma ramipril levels due to a diminished activity of esterases in the liver. In patients with impaired liver function, the use of **LIRACEN** is not recommended.

- Myocardial infarction and stroke have been reported and may relate to severe falls in blood pressure in patients with ischaemic heart disease or cerebrovascular disease.
- In volume depleted patients or patients with ischaemic heart disease or cerebrovascular disease, therapy should be monitored especially when the dose of **LIRACEN** or diuretic is adjusted.
- If hypotension occurs, the patient should be placed in the supine position and if necessary receive an intravenous infusion of 0,9 % saline.
- Increases in blood urea and serum creatinine have been seen in patients with no apparent pre-existing vascular disease, especially when **LIRACEN** has been given concomitantly with a diuretic. Dosage reduction or discontinuation of **LIRACEN** or the diuretic may be required.
- In patients undergoing surgery or during anaesthesia with agents producing hypotension, **LIRACEN** may block angiotensin II formation secondary to compensatory rennin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.
- ACE-inhibitors such as **LIRACEN** have been shown to be less effective as anti-hypertensives in black patients than in white patients.

Effects on ability to drive and use machine:

Treatment with **LIRACEN** may impair the ability to drive or operate machinery, especially at the start of treatment, when changing over from other preparations and during concomitant use of alcohol.

INTERACTIONS

Concomitant use of **LIRACEN** with:

- Loop, thiazide or related diuretics – “First dose hypotension” may occur (see **“DOSAGE AND DIRECTIONS FOR USE”**).

- Diuretics, alcohol and hypotension-producing medications - The antihypertensive effect is additive. It may be necessary to adjust the dose during concurrent use or when one medicine is discontinued.
- Potassium sparing diuretics such as spironolactone, triamterene or amiloride or potassium supplements – Concurrent administration may result in hyperkalaemia (see **"CONTRA-INDICATIONS"**). In patients with heart failure, potassium sparing diuretics should generally be stopped before starting **LIRACEN** therapy.
- Lithium – Increases in lithium concentrations have been reported (see **"CONTRA-INDICATIONS"**).
- Indomethacin and nonsteroidal anti-inflammatory medicines (NSAIDs) – reduce the antihypertensive effects of **LIRACEN**. Blood pressure monitoring should be increased when any NSAID is added or discontinued in a patient treated with **LIRACEN**.

PREGNANCY AND LACTATION

Safety in pregnancy and lactation has not been established (see **"CONTRA-INDICATIONS"**). **LIRACEN** can cause foetal morbidity and death.

LIRACEN crosses through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms. The use of **LIRACEN** during first trimester of pregnancy has been associated with an increased risk of birth defects, in particular of the cardiovascular and the central nervous system. Oligohydramnios as well as hypotension, oliguria and anuria in newborns, have been reported after administration of ramipril, such as contained in **LIRACEN** during the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur (See **"CONTRA-INDICATIONS"** and **"WARNINGS"**).

Teratogenicity has been shown in animals.

Hypertensive women receiving **LIRACEN** should take care to ensure that they do not become pregnant.

DOSAGE AND DIRECTIONS FOR USE

LIRACEN should be taken during or after meals with half a glass of liquid. In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of **LIRACEN**. The diuretic should, if possible, be discontinued for two to three days before starting

therapy with **LIRACEN** to reduce the likelihood of hypotension. If the diuretic therapy cannot be discontinued, the initial dose of **LIRACEN** should be 1,25 mg.

Hypertension:

Administration of **LIRACEN** to hypertensive patients results in a reduction of both supine and erect blood pressure. The antihypertensive effect is evident within one to two hours after intake of **LIRACEN**, peak effect occurs three to six hours after intake, and has been shown to be maintained for at least 24 hours at recommended doses. The dose range is 2,5 mg to 10 mg **LIRACEN** in a single daily dose.

The recommended initial dosage in patients not on diuretics is 2,5 mg **LIRACEN** once a day. Dosage should be increased to 5 mg **LIRACEN** and up to a maximum of 10 mg **LIRACEN** once a day, at intervals of one to two weeks, based on patient response. A maximum dose of 10 mg should not be exceeded.

Post-myocardial infarction:

The treatment with **LIRACEN** should be initiated in hospital 3 to 10 days after an acute myocardial infarction if the patient manifests with evidence of heart failure and is haemodynamically stable. The recommended dosage is 2,5 mg **LIRACEN** twice daily for two days. If well tolerated increase the dose to 5 mg **LIRACEN** twice daily. If patients are unable to tolerate **LIRACEN** 2,5 mg initially, 1,25 mg **LIRACEN** twice daily may be given initially and later increased to 2,5 mg twice daily.

Non-diabetic and diabetic nephropathy:

The recommended initial dose is 1,25 mg **LIRACEN** once daily.

Depending on how the patient tolerates **LIRACEN**, the dose should be increased.

It is recommended that the dose, if increased, be doubled at intervals of 2 to 3 weeks.

The maximum permitted daily dose is 10 mg **LIRACEN**.

In patients pre-treated with a diuretic, consideration must be given to discontinuing the diuretic for at least 2 to 3 days or depending on the duration of action of the diuretic, longer, before starting treatment with **LIRACEN**, or at least, to reducing the diuretic dose.

Dosage adjustment in renal impairment:

The use of **LIRACEN** in dialysis patients is not recommended.

To reduce the risk of myocardial infarction, stroke or cardiovascular death:

The recommended initial dose is 2,5 mg **LIRACEN** once daily.

Depending on the tolerability, the dose is gradually increased. The increase should be implemented by doubling the dose after one week of treatment. Three weeks later, it should be doubled again to the usual maintenance dose of 10 mg **LIRACEN** once daily.

SIDE-EFFECTS

Side-effects:

Blood and lymphatic system disorders:

Less frequent:

Decrease in white blood cell count, haemoglobin and haemocrit, bone marrow depression, anaemia, thrombocytopenia, agranulocytosis, haemolytic anaemia.

Immune system disorders:

Less frequent:

Hypersensitivity/angioedema reactions: Angioedema of the face, which may be fatal, extremities, lips, tongue, glottis and/or larynx and intestinal angioedema.

Metabolism and nutrition disorders:

Less frequent:

Hyperkalaemia, hyponatraemia, increases in blood urea, increases in serum creatinine.

Nervous system disorders:

Frequent:

Dizziness, headache, fatigue.

Less frequent:

Mood alterations, mental confusion, paraesthesia, vertigo, sleep disturbances.

Cardiac disorders

Less frequent:

Myocardial infarction, palpitations, tachycardia and chest pain.

Vascular disorders:

Less frequent:

Orthostatic effects including hypotension, cerebrovascular accident,

Respiratory, thoracic and mediastinal disorders:

Frequent:

A dry cough has been reported.

Less frequent:

Bronchospasm, rhinitis, sinusitis.

Gastrointestinal disorders:

Frequent:

Nausea, diarrhoea.

Less frequent:

Abdominal pain, indigestion, dry mouth, pancreatitis, vomiting and taste disturbances.

Hepato-biliary disorders:

Less frequent:

Hepatitis (hepatocellular or cholestatic) jaundice, increase in serum bilirubin, increase in liver enzymes.

Skin and subcutaneous tissue disorders:

Less frequent:

Rash, urticaria, diaphoresis, alopecia, pruritus, psoriasis, severe skin disorders including pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome and erythema multiforme.

Musculoskeletal, connective tissue and bone disorders:

Less frequent:

Asthenia.

Renal and urinary disorders:

Less frequent:

Uraemia, oliguria, anuria, renal dysfunction, acute renal failure.

Reproductive system and breast disorders:

Less frequent:

Impotence.

General disorders and administrative site conditions:

Less frequent:

A symptom complex has been reported which may include fever, vasculitis, myalgia, arthritis/arthralgia, positive antinuclear antibodies (ANA), elevated erythrocyte sedimentation rate, eosinophilia and leucocytosis. Rash, photosensitivity or other dermatological manifestations may occur.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Severe hypotension, electrolyte disturbances and renal failure are symptoms of overdose. Treatment is symptomatic and supportive. Treatment should include volume expanders.

IDENTIFICATION

LIRACEN 1,25 mg:

Yellow/White size ‘4’ hard gelatin capsules imprinted with ‘D’ on yellow cap and ‘40’ on white body with black edible ink filled with white to almost white powder.

LIRACEN 2,5 mg:

Orange/White size ‘4’ hard gelatin capsules imprinted with ‘D’ on orange cap and ‘41’ on white body with black edible ink filled with white to almost white powder.

LIRACEN 5 mg:

Red/White size ‘4’ hard gelatin capsules imprinted with ‘D’ on red cap and ‘42’ on white body with black edible ink filled with white to almost white powder.

LIRACEN 10 mg:

Blue/White size ‘4’ hard gelatin capsules imprinted with ‘D’ on blue cap and ‘43’ on white body with black edible ink filled with white to almost white powder.

PRESENTATION

LIRACEN 1,25 mg / LIRACEN 2,5 mg / LIRACEN 5 mg / LIRACEN 10 mg:

1. **Blister Packs:**

Capsules are packed in blister packs composed of cold form laminate: 60 micron PVC/ 25 micron OPA/ 60 micron aluminium foil/ 60 micron PVC film as the forming material and 25 micron Aluminum foil as the lidding material. One blister contains 10 capsules.

Pack size: 30's – Each carton contains 3 blisters of 10 capsules each.

Capsules are packed in blister packs composed of clear 250 micron PVC/ 25 micron PE/90 g/m^2 PVdC as the forming material and 25 micron aluminum foil as the lidding material. One blister contains 10 capsules.

Pack size: 30's – Each carton contains 3 blisters of 10 capsules each.

2. **HDPE Container Pack:**

Capsules are packed in 40 ml HDPE containers with polypropylene closures with induction sealing wad, containing 1 silica gel sachet. Each container contains 30 capsules.

Pack size: 30's - One HDPE container contains 30 capsules.

STORAGE INSTRUCTIONS:

Store at or below 25 °C.

Do not remove the blisters from the carton until required.

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBERS:

LIRACEN 1,25 mg: 44/7.1.3/1073

LIRACEN 2,5 mg: 44/7.1.3/1074

LIRACEN 5 mg: 44/7.1.3/1075

LIRACEN 10 mg: 44/7.1.3/1076

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Aurogen South Africa (Pty) Ltd

Woodhill Office Park, Building 1

53 Phillip Engelbrecht Avenue

Meyersdal, Ext. 12

1448

Johannesburg

South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

Date of registration:

27 November 2014

Date of revision:

06 December 2021