**APPROVED PROFESSIONAL INFORMATION**

## SCHEDULING STATUS

S3

## 1. NAME OF THE MEDICINE

**LISORETIC 10/12,5** tablets

**LISORETIC 20/12,5** tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LISORETIC 10/12,5: Each tablet contains lisinopril dihydrate equivalent to lisinopril 10 mg and hydrochlorothiazide 12,5 mg.

LISORETIC 20/12,5: Each tablet contains lisinopril dihydrate equivalent to lisinopril 20 mg and hydrochlorothiazide12,5 mg.

LISORETIC 10/12,5 contains sugar (mannitol 18,70 mg/tablet).

LISORETIC 20/12,5 contains sugar (mannitol 38,30 mg/tablet).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablets.

LISORETIC 10/12,5: A peach coloured, round, uncoated, biconvex tablet, debossed ‘LH’ on

one side and plain on the other.

LISORETIC 20/12,5: A white coloured, round, uncoated, biconvex tablet, debossed 'LH' on one side and score-line on the other.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

LISORETIC is indicated for the treatment of mild to moderate hypertension in patients who have been stabilised on their individual components, given in the same proportions.

### 4.2 Posology and method of administration

**Posology**

***Essential hypertension*:**

The usual dosage is one tablet daily, taken at approximately the same time each day. It is recommended that if the desired clinical effect cannot be achieved within 2 - 4 weeks with this dosage, the dosage may be increased to a maximum of two tablets, administered once daily.

***Prior treatment with diuretics:***

Symptomatic hypotension may occur after the initial dose of LISORETIC; this phenomenon is most likely to occur in patients who are volume and/or salt depleted as a result of prior diuretic therapy. If possible, the diuretic therapy should be discontinued for 2 - 3 days prior to initiation of therapy with LISORETIC, or if this is not possible, lisinopril should be given

alone at a low initial dose of 5 mg.

**Special populations**

***Renal impairment:***

Hydrochlorothiazide may not be a suitable diuretic for use in patients with mild to moderate renal impairment. Hydrochlorothiazide is contraindicated in severe renal impairment (creatinine clearance values of 30 mL/min or below) (see section 4.3). LISORETIC should not be used as initial therapy in any patient with renal insufficiency. In patients with creatinine clearance of >30 and <80 mL/min, LISORETIC may be used, but only after titration of the individual components.

***Use in the elderly:***

There is no significant difference in the efficacy and tolerability to lisinopril and hydrochlorothiazide, administered concomitantly, between elderly and younger hypertensive patients.

**Paediatric population**

Safety and efficacy in children have not been established.

**Method of administration**

For oral use. Swallow the tablet with a drink of water.

### Missed dose

Medical practitioners should advise patients who forget to take LISORETIC to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the missed dose.

### 4.3 Contraindications

LISORETIC is contraindicated in:

- hypersensitivity to lisinopril, hydrochlorothiazide or to any of the ingredients of LISORETIC
- patients with a history of previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and lip
- hypersensitivity to sulphonamides and sulphonamide-derived medicines
- a history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs). Such patients must never again be given these medicines
- hereditary or idiopathic angioedema (see section 4.4)
- hypertrophic obstructive cardiomyopathy (HOCM)
- severe renal function impairment (creatinine clearance less than 30 mL/min)
- anuria
- 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
- hydrochlorothiazide, as in LISORETIC, should not be given to patients with Addison's disease
- lithium therapy: concomitant administration with LISORETIC may lead to toxic blood concentrations of lithium
- severe hepatic impairment
- concomitant administration with renin inhibitors such as aliskiren-containing medicines
- the concomitant use of ACE inhibitors with fluoroquinolones is contraindicated in patients with moderate to severe renal impairment (creatinine ≤ 30 mL/min) and in the elderly patients. (see sections 4.4 and 4.5)
- concomitant use of LISORETIC with sacubitril/valsartan therapy. LISORETIC must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.4 and 4.5)
- pregnancy and lactation.

## 4.4 Special warnings and precautions for use

**Should a woman become pregnant while receiving LISORETIC, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see sections 4.3 and 4.6).**

**Renal transplantation**

LISORETIC should not be administered, since there is no experience with patients recently transplanted with a kidney.

**Anaphylactoid reactions in haemodialytic patients**

The use of LISORETIC is not indicated in patients requiring dialysis for renal failure. Anaphylactoid reactions have been reported in patients, undergoing haemodialysis procedures with certain dialysis membranes (e.g. with the high-flux membranes AN 69 and during low-density lipoprotein apheresis with dextran sulphate) and concurrent treatment with an ACE inhibitor. Consideration to the use of a different type of dialysis membrane or a different class of antihypertensive medicine should be given in these patients.

**Aortic and mitral valve stenosis / hypertrophic cardiomyopathy**

LISORETIC should not be given to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle, such as aortic stenosis or hypertrophic cardiomyopathy (see section 4.3).

**Dual blockade of the renin-angiotensin-aldosterone system (RAAS) with aliskiren-containing medicines**

Dual blockade of the renin-angiotensin-aldosterone system by combining lisinopril with renin inhibitors such as aliskiren is contraindicated since there is an increased risk of hypotension, hyperkalaemia and changes in renal function (see sections 4.3 and 4.5).

### Renal insufficiency

Hydrochlorothiazide, as in LISORETIC, may not be a suitable diuretic for use in patients with renal impairment and is ineffective at creatinine clearance values of 30 mL/min or below (i.e. severe renal insufficiency). LISORETIC should not be administered to patients with a creatinine clearance ≤ 80 mL/min until titration of the individual components has shown the need for the doses present in LISORETIC.

In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have received ACE inhibitor treatment, increases in blood urea and serum creatinine, which may be reversible upon discontinuation of therapy, have been seen. This is especially likely to occur in patients with renal insufficiency.

Some hypertensive patients with no apparent pre-existing renal disease have developed increases in blood urea and serum creatinine, when lisinopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or lisinopril may be required. LISORETIC is contraindicated in severe renal impairment (<30 mL/min) (see section 4.3)

The concomitant use of ACE inhibitors such as LISORETIC and fluoroquinolones**,** may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment (creatinine ≤ 30 mL/min) and in elderly patients. (See sections 4.3 and 4.5). Renal function should be assessed before initiating treatment with concomitant use of with ACE-inhibitors and fluoroquinolones.

**Prior diuretic therapy**

Previous diuretic therapy should be discontinued for 2-3 days prior to initiation with LISORETIC. If this is not possible, treatment should be started with lisinopril alone, in a 5 mg dose.

**Anaphylactoid reactions related to low-density lipoproteins (LDL) apheresis**

Patients treated with ACE inhibitors such as in LISORETIC during low-density lipoprotein (LDL) apheresis with dextran sulphate have shown life threatening anaphylactic reactions. These symptoms could be avoided by temporary discontinuation of the treatment with ACE inhibitors before each apheresis.

**Hepatic disease**

Caution should be exercised when hydrochlorothiazide is used in patients with hepatic impairment or progressive liver disease, as minor alterations of fluid and electrolyte balance may precipitate hepatic coma in these patients. LISORETIC is contraindicated in severe hepatic impairment (see section 4.3)**.**

Patients receiving LISORETIC, who develop jaundice or marked elevations of hepatic enzymes should discontinue LISORETIC and receive appropriate medical follow-up.

**Non-melanoma skin cancer**

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies. Photosensitising

actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking LISORETIC should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventative measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimise the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. LISORETIC should not be used by patients who have had previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin /or lip (see section 4.3)**.** The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC.

**Surgery/anaesthesia**

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

**Metabolic and endocrine effects**

ACE inhibitors, such as lisinopril, and hydrochlorothiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic medicines, including insulin, may be required. Increased cholesterol and triglyceride levels may be a result of hydrochlorothiazide diuretic therapy.

Hydrochlorothiazide may precipitate hyperuricaemia and/or gout in certain patients. Due to

the increase in urinary uric acid caused by lisinopril, hyperuricaemia may be attenuated by LISORETIC which contains both components.

**Hypotension and electrolyte/fluid imbalance**

Symptomatic hypotension has been seen in uncomplicated hypertensive patients, but is more likely to occur if the patient has been volume-depleted, e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin-dependant hypertension (see sections 4.4 and 4.5).

Determination of serum electrolytes should be performed at appropriate intervals in such patients. Initiation of treatment and dose adjustment should be monitored under close medical supervision in patients with an increased risk of symptomatic hypotension. Particular consideration applies to patients with ischaemic heart or cerebrovascular disease as an excessive decrease in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of 0.9 % normal saline. A transient hypotensive response does not warrant discontinuation of further doses.

Following restoration of effective blood volume and pressure, therapy at a reduced dosage may be reinstituted; or alternatively either of the individual components may be used separately. In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with LISORETIC. This effect is anticipated and is not usually a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of LISORETIC may be necessary.

**Electrolyte imbalance**

Periodic determination of serum electrolytes should be performed at appropriate intervals. Hydrochlorothiazide can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia, and hypochloraemic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, weakness, lethargy, drowsiness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting. Dilutional hyponatraemia may occur in oedematous patients in hot weather. Chloride deficit is generally mild and does not require treatment. Hydrochlorothiazide has been shown to increase the urinary excretions of magnesium, which may result in hypomagnesaemia.

Decreased urinary calcium excretion caused by hydrochlorothiazide may result in intermittent and a slightly raised serum calcium concentration. Should marked hypercalcaemia occur, it may be evidence of underlying hyperparathyroidism. LISORETIC therapy should be discontinued before carrying out tests for parathyroid function (see section 4.5).

**Hyperkalaemia**

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including lisinopril as in LISORETIC.

The concomitant use of potassium sparing diuretics is contraindicated (see section 4.3). Patients at risk of developing hyperkalaemia include those with renal insufficiency, diabetes mellitus, or those using concomitant potassium supplements or potassium-containing salt substitutes, or those patients taking other medicines associated with increases in serum

potassium (e.g. heparin).

If concomitant use of the above-mentioned medicines is deemed appropriate, an increased monitoring of serum potassium is recommended (see section 4.5).

**Hypersensitivity/angioedema**

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including lisinopril. In such cases LISORETIC should be discontinued immediately and appropriate measures should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. In instances where swelling has been confined only to the face and lips, the condition may resolve without treatment, although antihistamines have been useful in relieving symptoms. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with anti-histamines and corticosteroids may not be sufficient. 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 maintenance of a patient 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.

Patients with a history of angioedema unrelated to ACE-inhibitor therapy may be at increased risk of angioedema while receiving an ACE-inhibitor as in LISORETIC (see section 4.3).

In patients receiving hydrochlorothiazide as in LISORETIC, sensitivity reactions may occur

with or without a history of allergy or bronchial asthma.

Due to the increased risk of angioedema, concomitant use of LISORETIC with sacubitril/valsartan is contraindicated. Sacubitril/valsartan treatment must not be initiated earlier than 36 hours after the last dose of LISORETIC. LISORETIC therapy must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5).

Concomitant use of LISORETIC with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin in a patient already taking LISORETIC.

**Systemic lupus erythematosus**

Exacerbation or activation of systemic lupus erythematosus has been reported with the use of hydrochlorothiazide.

**Desensitisation**

Patients receiving ACE-inhibitors, such as in LISORETIC, during desensitisation treatment (e.g. hymenoptera venom) have sustained anaphylactoid reactions. These reactions may be avoided when LISORETIC is temporarily withheld but may reappear upon inadvertent re-challenge.

**Neutropenia/agranulocytosis**

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported for patients receiving ACE inhibitors as in LISORETIC. In patients with normal renal function and no other complicating factors neutropenia occurs less frequently. Neutropenia and agranulocytosis are reversible after discontinuation of the ACE inhibitor. Lisinopril, as in LISORETIC, 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.

**Cough**

A non-productive, persistent cough has been reported with the use of ACE inhibitors including lisinopril. The cough may usually resolve after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

**Lithium**

The combination of ACE inhibitors and lithium is contraindicated (see sections 4.3 and 4.5).

**Anti-doping test**

The hydrochlorothiazide contained in LISORETIC could produce a positive analytic result in

an anti-doping test.

**Photosensitivity**

Cases of photosensitivity reactions have been reported with hydrochlorothiazide (see section 4.8). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of LISORETIC is deemed necessary, it is recommended to protect exposed areas from the sun or artificial UVA.

**Porphyria**

Safety of hydrochlorothiazide in porphyria has not been established (see section 4.3).

**Acute angle-closure glaucoma**

Hydrochlorothiazide, a sulphonamide, as contained in LISORETIC has been associated with an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of LISORETIC initiation.

Untreated acute angle-closure glaucoma can lead to permanent vision loss. Primarily, treatment with hydrochlorothiazide, as in LISORETIC, must be discontinued as rapidly as possible. Prompt medical or surgical treatment may need to be considered if the intraocular pressure remains uncontrolled.

Risk factors for developing acute angle-closure glaucoma may include a history of sulphonamide or penicillin allergy (see section 4.8).

**Patient populations**

*Ethnic groups*

LISORETIC causes a higher rate of angioedema in black patients than in non-black patients. Lisinopril may be less effective in lowering blood pressure in black patients than in non-black patients, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

**Information on excipients of LISORETIC**

LISORETIC contains less than 1 mmol (0,023 g) sodium per tablet, that is to say essentially 'sodium free'.

**Paediatric population**

Safety and efficacy have not yet been established in children.

**4.5 Interaction with other medicines and other forms of interaction**

- dual blockade of the renin-angiotensin-aldosterone system by combining lisinopril with renin inhibitors is contraindicated since there is an increased risk of hypotension, hyperkalaemia and changes in renal function. The combination of LISORETIC with renin inhibitors is contraindicated (see section 4.3)
- increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. The combination of LISORETIC with lithium is contraindicated (see sections 4.3 and 4.4)

- concomitant use of ACE inhibitors such as LISORETIC with fluoroquinolones (e.g ciprofloxacin, moxifloxacin and levofloxacin) may precipitate acute kidney injury (see sections 4.3 and 4.4)
- concomitant use of LISORETIC with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see section 4.3 and 4.4)
- concomitant use of LISORETIC with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increase in the risk of angioedema (see section 4.4)
- concomitant treatment with tissue plasminogen activators may increase the risk of angioedema
- the decrease in potassium caused by hydrochlorothiazide diuretics is usually attenuated by the effect of lisinopril. The use of potassium supplements, potassium-sparing agents or potassium-containing salt substitutes, especially in patients with impaired renal function, may result in a significant increase in serum potassium (see section 4.4)
- because of the risk of hypokalaemia the concomitant administration of hydrochlorothiazide and medicines that induce Torsades de pointes, e.g. some antidysrhythmics, some antipsychotics and other medicines known to induce Torsades de pointes, should be used with caution
- concomitant use of certain anaesthetic medicines, tricyclic antidepressants and antipsychotics with ACE inhibitors, as in LISORETIC, may result in further lowering of blood pressure
- diuretics and other hypertensive medicines may increase the hypotensive effects

- chronic administration of nonsteroidal anti-inflammatory drugs (NSAIDs) (selective cyclooxygenase-2 inhibitors, acetylsalicylic acid (aspirin) >3 g/day and non-selective NSAIDs) may reduce the antihypertensive and diuretic effect of ACE inhibitors and hydrochlorothiazide, as in LISORETIC. NSAIDs and ACE inhibitors may exert an additive effect on the increase in serum potassium and may result in a deterioration of renal function. These effects may be reversible. Acute renal failure may occur, especially in patients with compromised renal function such as the elderly or dehydrated
- 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 LISORETIC therapy
- sympathomimetics may antagonise the antihypertensive effect of ACE inhibitors such as LISORETIC
- epidemiological studies indicate that concomitant administration of ACE inhibitors, as in LISORETIC, and antidiabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood glucose lowering effect with risk of hypoglycaemia. This phenomenon appears to be more likely during the first weeks of combination treatment and in patients with renal impairment
- concomitant use of hydrochlorothiazide and corticosteroids, or adrenocorticotropic hormone (ACTH) may intensify electrolyte depletion and hypokalaemia
- increased serum calcium levels due to decreased excretion may occur when administered concurrently with hydrochlorothiazide, as in LISORETIC. In cases where

calcium or vitamin D must be prescribed, serum calcium levels should be monitored and the dose accordingly adjusted

- hydrochlorothiazide may decrease response to pressor amines. This decrease in response is not sufficient to preclude the use of pressor amines
- the effect of non-depolarising muscle relaxants (e.g. tubocurarine chloride) may be potentiated by hydrochlorothiazide, as in LISORETIC
- concomitant administration of ACE inhibitors and hydrochlorothiazide, as in LISORETIC, with trimethoprim increases the risk of hyperkalaemia
- hydrochlorothiazide-induced hypokalaemia can increase the risk of sotalol-induced dysrhythmia
- concomitant administration of LISORETIC and allopurinol increases the risk of renal damage and can lead to an increased risk of leucopaenia
- concomitant administration of LISORETIC and ciclosporin increases the risk of renal damage and hyperkalaemia as well as increase the risk of hyperuricaemia and gout-type complications
- concomitant administration of LISORETIC and lovastatin increases the risk of hyperkalaemia
- cytostatics, immune-suppressives, procainamide – concomitant administration of LISORETIC can lead to increased risk of leucopaenia
- alcohol, barbiturates or narcotics: Potentiation of orthostatic hypotension may occur
- hydrochlorothiazide may intensify electrolyte imbalance, particularly hypokalaemia during concomitant use of amphotericin B (parenteral), carbenoxolone, corticosteroids, corticotropin (ACTH) or stimulant laxatives

- concomitant use of hydrochlorothiazide with digoxin increases the risk of digitalis toxicity associated with hydrochlorothiazide-induced hypokalaemia
- cholestyramine and colestipol may delay or reduce absorption of hydrochlorothiazide Therefore, LISORETIC should be taken at least 1 hour before or 4 - 6 hours after intake of these medicines
- thiazides may increase the risk of adverse effects caused by amantadine.

## 4.6 Fertility, pregnancy and lactation

### Pregnancy

LISORETIC is contraindicated in pregnancy and lactation (see section 4.3). LISORETIC can cause foetal morbidity and death. LISORETIC passes through the placenta and can 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 LISORETIC in the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur. In addition, use of LISORETIC during the first trimester of pregnancy has been associated with an increased risk of birth defects, in particular of the cardiovascular and the central nervous system (see sections 4.3 and 4.4).

### Breastfeeding

It is not known whether lisinopril is distributed into human breast milk. Hydrochlorothiazide does appear in human milk.

Because of the potential for adverse effects on the infant, mothers on LISORETIC should not breastfeed their infants (see section 4.8).

### Fertility

There is no fertility data with LISORETIC.

### 4.7 Effects on ability to drive and use machines

LISORETIC may have a mild to moderate influence on the ability to drive and use machines. Especially at the start of the treatment or when the dose is modified, and also when used in combination with alcohol, but these affects depend on the individual's susceptibility.
LISORETIC can cause side effects such as dizziness or tiredness.
During LISORETIC administration, patients should be cautioned about re-engaging in activities requiring rapid and precise responses such as driving a vehicle or operating machinery.

### 4.8 Undesirable effects

***a. Summary of the safety profile***

The most commonly reported adverse effects with the lisinopril/hydrochlorothiazide combination are cough, fatigue, dizziness, hypotension, including orthostatic hypotension and headache.
Less common were diarrhoea, nausea, vomiting, dry mouth, rash, gout, palpitations, chest discomfort, muscle cramps and weakness, paraesthesia, asthenia and impotence.

Adverse events reported with the individual components, lisinopril and hydrochlorothiazide may be potential adverse effects with LISORETIC. Adverse effects of the individual components are detailed below.

### *b. Tabulated list of adverse reactions*

### *LISORETIC – Post-marketing:*

| **System Organ Class** | **Frequency** | **Side effects** |
|---|---|---|
| Blood and lymphatic system disorders | Less frequent | Anaemia, bone marrow depression, thrombocytopaenia, leucopaenia, agranulocytosis, haemolytic anaemia |
| Immune system disorders | Frequency unknown | Anaphylactic/anaphylactoid reaction |
| Endocrine disorders | Less frequent | Inappropriate antidiuretic hormone secretion |
| Metabolism and nutrition disorders | Less frequent | Hyperglycaemia, hypokalaemia, hyperuricaemia, hyperkalaemia, gout |
| Psychiatric disorders | Less frequent | Depressive symptoms |
| Nervous system disorders | Frequent<br><br>Less frequent | Dizziness, headache, paraesthesia<br>Olfactory disturbance |
| Cardiac disorders | Frequent<br><br>Less frequent | Orthostatic effects (including hypotension), syncope<br>Palpitations |
| Respiratory, thoracic and mediastinal disorders | Frequent | Cough |
| Gastrointestinal disorders | Less frequent | Diarrhoea, nausea, vomiting<br>Dry mouth, pancreatitis, intestinal angioedema |

| | | |
|---|---|---|
| Hepatobiliary disorders | Less frequent | Hepatitis – either hepatocellular or cholestatic, jaundice, hepatic failure. Very rarely, it has been reported that in some patients the undesirable development of hepatitis has progressed to hepatic failure. Patients receiving LISORECTIC who develop jaundice or marked elevation of hepatic enzymes should discontinue LISORETIC and receive appropriate medical follow up. |
| Skin and subcutaneous tissue disorders | Frequent<br>Less frequent<br><br><br><br><br><br>Frequency unknown | Rash<br>Hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx (see section 4.3 and section 4.4), cutaneous pseudolymphoma<br>A symptom complex has been reported which may include one or more of the following: fever, vasculitis, myalgia, arthralgia/ arthritis, a positive antinuclear antibodies (ANA), elevated red blood cell sedimentation rate (ESR), eosinophilia and leucocytosis, rash, photosensitivity or other dermatological manifestations may occur. |

| | | |
|---|---|---|
| Musculoskeletal, connective tissue and bone disorders | Frequent<br>Less frequent | Muscle cramps<br>Muscle weakness |
| Reproductive system and breast disorders | Frequent | Impotence |
| General disorders and administrative site conditions | Frequent<br>Less frequent | Fatigue, asthenia<br>Chest discomfort |
| Investigations | Frequent<br><br><br><br>Less frequent | Increases in blood urea, increases in serum creatinine, increases in liver enzymes, decreases in haemoglobin<br>Decreases in haematocrit, increases in serum bilirubin |

***Lisinopril:***

| **System Organ Class** | **Frequency** | **Side effects** |
|---|---|---|
| Blood and lymphatic system disorders | Less frequent | Bone marrow depression, anaemia, thrombocytopaenia, leucopaenia, agranulocytosis, neutropenia, haemolytic anaemia, lymphadenopathy |
| Immune system disorders | Less frequent | Hypersensitivity/ angioedema of the face, extremities, lips, tongue, glottis and/or larynx, skin rash, photosensitivity, alopecia, autoimmune disease |
| Endocrine disorders | Less frequent | Syndrome of inappropriate antidiuretic hormone Secretion (SIADH) |

| | | |
|---|---|---|
| Metabolism and nutrition disorders | Less frequent | Gout, hyperglycaemia, hypokalaemia, hyperuricaemia hyperkalaemia, pancreatitis, hyponatraemia, hypoglycaemia |
| Psychiatric disorders | Less frequent | Mood alterations, mental confusion, depressive symptoms, sleep disturbances, olfactory disturbance, hallucinations |
| Nervous system disorders | Frequent<br>Less frequent | Dizziness, headache<br>Paraesthesia, asthenia, fatigue, syncope, vertigo, taste disturbance, hypoaesthesia |
| Cardiac disorders | Less frequent | Myocardial infarction or cerebrovascular accident, tachycardia, palpitations, chest pain |
| Vascular disorders | Less frequent | Orthostatic effects (including orthostatic hypotension), Raynaud's syndrome, flushing |
| Respiratory, thoracic and mediastinal disorders | Frequent<br>Less frequent | Cough<br>Bronchospasm, rhinitis, sinusitis, pulmonary infiltrates, allergic alveolitis/eosinophilic pneumonia |
| Gastrointestinal disorders | Less frequent | Nausea, gastrointestinal disturbances, stomatitis, abdominal pain, indigestion, diarrhoea, vomiting, dry mouth, intestinal angioedema, pancreatitis |
| Hepatobiliary disorders | Less frequent | Hepatitis (hepatocellular or cholestatic), jaundice, elevated liver enzymes and bilirubin, hepatic failure |

| | | |
|---|---|---|
| Skin and subcutaneous tissue disorders | Less frequent | Hypersensitivity/ angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx, pruritus, urticaria, psoriasis and severe skin disorders, including pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme, alopecia, diaphoresis, cutaneous pseudo-lymphoma*, skin rash |
| Musculoskeletal, connective tissue and bone disorders | Less frequent | Muscle cramps |
| Renal and urinary disorders | Less frequent | Diaphoresis, uraemia, oliguria/anuria, renal dysfunction, acute renal failure, proteinuria |
| Reproductive system and breast disorders | Less frequent | Impotence, gynaecomastia |
| General disorders and administrative site conditions | Less frequent | Asthenia, fatigue |

*A symptom complex has been reported which may include one or more of the following: fever, vasculitis, myalgia, arthralgia/arthritis, a positive antinuclear antibodies (ANA), elevated red blood cell sedimentation rate (ESR), eosinophilia and leucocytosis, rash, photosensitivity or other dermatological manifestations may occur.

***Hydrochlorothiazide:***

Adverse events reported with the use of hydrochlorothiazide alone include

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| **System Organ Class** | **Frequency** | **Side effects** |
|---|---|---|
| Infections and infestations | Frequency unknown | Sialadenitis |
| Neoplasms benign and malignant (including cysts and polyps) | Frequency unknown | Non -melanoma skin cancer (basal cell carcinoma, squamous cell carcinoma) |
| Blood and lymphatic system disorders | Less frequent | leucopaenia, agranulocytosis, thrombocytopaenia, aplastic anaemia, haemolytic anaemia, granulocytopenia, bone marrow depression |
| Immune system disorders | Less frequent | Hypersensitivity reaction (rash, fever, pulmonary oedema, pneumonitis, anaphylaxis) |
| Metabolism and nutrition disorders | Frequent<br>Less frequent | Electrolyte imbalance<br>Anorexia, hyperuricaemia, gout, cholecystitis, hyperglycaemia, glycosuria, hyperuricaemia, hypomagnesaemia, increases in cholesterol and triglycerides, hyponatremia, hypokalaemia, hypochloraemic alkalosis |
| Psychiatric disorders | Less frequent | Restlessness, depression |
| Nervous system disorders | Frequent | Fever, paraesthesia, hypoaesthesia, light-headedness, dizziness, headache, sleep disturbances |

| | | |
|---|---|---|
| Eye disorders | Less frequent<br><br><br><br>Frequency unknown | Xanthopsia, transient blurred vision, yellow vision, acute myopia, acute angle-closure glaucoma<br>Choroidal effusion |
| Ear and labyrinth disorders | Frequency unknown | Vertigo |
| Cardiac disorders | Less frequent | Postural hypotension |
| Vascular disorders | Less frequent | Orthostatic hypotension, necrotisin angiitis (vasculitis, cutaneous vasculitis) |
| Respiratory, thoracic and mediastinal disorders | Frequent | Respiratory distress (including pneumonitis and pulmonary oedema) |
| Gastrointestinal disorders | Frequent<br>Less frequent | Gastric irritation, constipation<br>Gastrointestinal disturbances, nausea, vomiting, diarrhoea, sialadenitis, intestinal ulceration, pancreatitis |
| Hepatobiliary disorders | Less frequent | Jaundice (intrahepatic cholestatic jaundice) |
| Skin and subcutaneous tissue disorders | Frequent<br>Less frequent | Skin rash<br>Purpura, photosensitivity, urticaria**,** toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, systemic lupus erythematosus |

| | | |
|---|---|---|
| Musculoskeletal, connective tissue and bone disorders | Frequent<br>Less frequent | Muscle spasm<br>Muscle weakness, muscle pain and cramps |
| Renal and urinary disorders | Less frequent | Renal dysfunction, renal failure, interstitial nephritis, non-opaque urate calculi |
| Reproductive system and breast disorders | Less frequent | Sexual dysfunction |
| General disorders and administrative site conditions | Less frequent | Fever, weakness |

*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. Healthcare professionals are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

## 4.9 Overdose

Signs and symptoms:

Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough. The most common signs and

symptoms of hydrochlorothiazide overdose observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatremia) and dehydration resulting from excessive diuresis.

If digitalis has been used concomitantly, hypokalaemia may accentuate cardiac dysrhythmias.

Management of overdose:

Treatment is symptomatic and supportive. No specific information is available on the treatment of overdosage with LISORETIC. Therapy with LISORETIC should be discontinued and the patient should be kept under very close supervision. Suggested measures include induction of emesis, if ingestion is recent, and correction of dehydration, electrolyte imbalance and hypotension by established procedures.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin converting enzyme inhibitor and thiazide diuretic

ATC code: C09B A03

Pharmacological classification: A 7.1.3 Other hypotensives.

LISORETIC is a fixed dose combination product of an angiotensin converting enzyme (ACE) inhibitor, lisinopril and a diuretic, hydrochlorothiazide. Both components have complementary modes of action and exert an additive antihypertensive effect.

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## Lisinopril

Mechanism of action:

Lisinopril is a peptidyl dipeptidase inhibitor and inhibits the angiotensin converting enzyme (ACE) that catalyses the conversion of angiotensin I to angiotensin II. Angiotensin II is a vasoconstrictor peptide which 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. Reduced aldosterone secretion may result in an increase in serum potassium concentration. The mechanism of action through which lisinopril lowers blood pressure is mainly via suppression of the renin-angiotensin-aldosterone system; however, lisinopril also has antihypertensive effects in patients with low-renin hypertension. ACE is identical to kininase II, an enzyme that degrades bradykinin. It could be possible that increased levels of bradykinin, a potent vasodilatory peptide, play a role in the therapeutic effects of lisinopril. However, this remains to be elucidated.

## Hydrochlorothiazide

Mechanism of action:

Hydrochlorothiazide is a diuretic and an antihypertensive medicine. It affects the distal renal tubular mechanism of electrolyte re-absorption and increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate. The mechanism of the antihypertensive effects of hydrochlorothiazide is unknown. Hydrochlorothiazide does not usually affect normal blood pressure.

## 5.2 Pharmacokinetic properties

The concomitant administration of lisinopril and hydrochlorothiazide has no clinically significant effect on the pharmacokinetics of either medicine.

### Lisinopril

**Absorption:**

Lisinopril is absorbed slowly, variably and incompletely after oral administration. Following oral administration of lisinopril, peak serum concentrations occur within about 7 hours. The mean extent of absorption of lisinopril is approximately 25 %, based on urinary recovery. The absorption varies between individuals (6-60 %) over the dose range 5 mg -80 mg. In patients with heart failure the absolute bioavailability is reduced by approximately 16 %. The absorption of lisinopril is not affected by the presence of food in the gastrointestinal tract.

**Distribution:**

Lisinopril does not appear to bind to other serum proteins other than to circulating angiotensin-converting enzymes (ACE).

**Elimination:**

Lisinopril does not undergo metabolism and the absorbed medicine is excreted unchanged entirely in the urine. Lisinopril has an effective half-life of accumulation of 12,6 hours on multiple dosing. In healthy subjects the clearance of lisinopril is approximately 50 mL/min. A prolonged terminal phase, is shown by declining serum concentrations, probably represented by saturable binding to ACE and is not proportional to dose.

## Pharmacokinetics in special patient groups

### Hepatic impairment

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

### 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.

**Table 1 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 | **$C_{max}$ (ng/mL)** | **$T_{max}$ (hr)** | **AUC (0-24 hrs) (ng/hr/mL)** | **$t_{1/2}$ (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 |

Mean AUC was increased by 13 % only, with a creatinine clearance of 30-80 mL/min, while a 4 - 5-fold increase in mean AUC was observed with creatinine clearance of 5-30 mL/min. Lisinopril can be removed by dialysis. Plasma lisinopril concentrations decreased on average by 60 % during 4 hours of haemodialysis, with a dialysis clearance between 40 and 55 mL/min.

### Heart Failure

When compared to healthy subjects, patients with heart failure have a greater exposure of

lisinopril (on average an increase in AUC of 125 %). However, there is reduced absorption of approximately 16 % compared to healthy subjects (based on the urinary recovery of lisinopril).

**Elderly**

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

**Hydrochlorothiazide**

The plasma half-life of hydrochlorothiazide can vary between 5,6 - 14,8 hours. Approximately 61 % of the dose is eliminated unchanged within 24 hours.

After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts 6 - 12 hours. Hydrochlorothiazide does cross the placental but not the blood-brain barrier.

### 5.3 Preclinical safety data

Lisinopril and hydrochlorothiazide are both medicines on which extensive clinical experience has been obtained, both separately and in combination. All relevant information for the prescriber is provided elsewhere in the Professional Information.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Croscarmellose sodium

Dibasic calcium phosphate dihydrate

Magnesium stearate

Mannitol

Pregelatinised maize starch

The following colourants are also used in the 10/12,5 mg tablet only: iron oxide red, iron oxide yellow.

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

36 months.

## 6.4 Special precautions for storage

Store at or below 25 ºC. Protect from light.

Do not remove blister from the carton until required for use.

## 6.5 Nature and contents of container

LISORETIC 10/12,5: PVC/PVDC/aluminium blister packs of 30 tablets, contained in a printed outer carton.

LISORETIC 20/12,5: PVC/PVDC/aluminium blister packs of 30 tablets, contained in a printed outer carton.

### 6.6 Special precautions for disposal

No special requirements

## 7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

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Silverwood Close

Westlake, Cape Town

7945, South Africa

Tel: +27 21 707 7000

or 0860-PHARMA (742 762)

## 8. REGISTRATION NUMBER(S)

LISORETIC 10/12,5: A37/7.1.3/0475

LISORETIC 20/12,5: A37/7.1.3/0476

## 9. DATE OF FIRST AUTHORISATION

Date of registration: 11 February 2005

## 10. DATE OF REVISION OF THE TEXT

03 March 2025

**APPROVED PROFESSIONAL INFORMATION**

**NAMIBIA**

LISORETIC 10/12,5: NS2 06/7.1.3/0063

LISORETIC 20/12,5: NS2 06/7.1.3/0064

**MOZAMBIQUE**

LISORETIC 10/12,5: 4648

LISORETIC 20/12,5: 4649

**ZAMBIA**

LISORETIC 10/12,5: POM 051/021

LISORETIC 20/12,5: POM 051/020