Approved Professional Information for Medicines for Human Use: LISOZIDE 10/20

SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

LISOZIDE-10 tablets

LISOZIDE-20 tablets

COMPOSITION

LISOZIDE-10:

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

LISOZIDE-20:

Each tablet contains lisinopril dihydrate equivalent to lisinopril 20 mg and hydrochlorothiazide 12,5 mg.

Excipients

Calcium hydrogen phosphate, magnesium stearate, maize starch, maize starch (dried), mannitol, pregelatinized starch.

Ferric oxide red and ferric oxide yellow is present in **LISOZIDE-10.**

LISOZIDE is sugar free.

CATEGORY AND CLASS

A 7.1.3: Other hypotensives.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Lisinopril/HCTZ is a combination of an angiotensin converting enzyme inhibitor, lisinopril and a diuretic, hydrochlorothiazide. Both these components have been widely used alone and in combination for the treatment of hypertension due to additive effects. 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, plays a role in the therapeutic effects of lisinopril. However, this remains to be elucidated.

Hydrochlorothiazide is a thiazide diuretic and an antihypertensive agent. 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 the thiazides is unknown. Thiazides do not usually affect normal blood pressure.

Pharmacokinetic properties

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

Lisinopril

Approximately 60 % of lisinopril is absorbed after oral administration. The absorption varies between individuals (6 to 60 %).

Following oral administration of lisinopril, peak serum concentrations occur within about 7 hours. Lisinopril has an effective half-life of 12 hours. Lisinopril does not bind to other serum proteins.

The absorption of lisinopril is not affected by the presence of food in the gastro-intestinal tract.

Lisinopril does not undergo metabolism and absorbed drug is excreted unchanged entirely in the urine. Impaired renal function decreases elimination of lisinopril. This decrease only becomes clinically important when the glomerular filtration rate is below 30 ml/min. Lisinopril can be removed by dialysis.

Older patients have higher blood levels and higher values for the area under the plasma concentration time curve than younger patients.

Hydrochlorothiazide

The plasma half-life of hydrochlorothiazide can vary between 5 and 15 hours. Approximately 60 % 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 to 12 hours.

INDICATIONS

Mild to moderate hypertension in patients who have been stabilized on their individual components given in the same proportions.

CONTRAINDICATIONS

LISOZIDE is contraindicated in the following circumstances:

- Hypersensitivity to any of the ingredients of **LISOZIDE.**
- Hypersensitivity to any other angiotensin converting enzyme (ACE) inhibitor.

- Hypersensitivity to any sulphonamide-derived medicines.
- Anuria.
- History of angioedema relating to previous treatment with an angiotensin-converting enzyme (ACE) inhibitor.
- Hereditary or idiopathic angioedema (see Special Precautions).
- Pregnancy and lactation– (see Human Reproduction)
- Patients with aortic stenosis or hypertrophic obstructive cardiomyopathy (HOCM).
- Bilateral renal artery stenosis or unilateral renal artery stenosis in the presence of single kidney.
- Severe renal impairment (creatinine clearance <30 ml/min).
- Severe hepatic impairment.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene and amiloride (see INTERACTIONS).
- Lithium therapy: Concomitant administration with LISOZIDE may lead to toxic blood concentrations of lithium (see INTERACTIONS).
- The concomitant use of **LISOZIDE** with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1,73 m^2) (see INTERACTIONS).
- Concomitant use of **LISOZIDE** with fluoroquinolones in patients with moderate to severe renal impairment.

WARNINGS AND SPECIAL PRECAUTIONS

Should a woman become pregnant while receiving **LISOZIDE,** the treatment must be stopped immediately and switched to an alternative medicine. Should a woman contemplate pregnancy, an alternative antihypertensive medication should be used (see HUMAN REPRODUCTION).

- There is an increased risk in non-melanoma skin cancer (NMSC) (basal cell carcinoma, squamous cell carcinoma) with exposure to increasing cumulative doses of hydrochlorothiazide.
- Patients taking **LISOZIDE** should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions as well as changes to existing ones, and to report any suspicious skin lesions, which should be examined.
- Exposure to sunlight and ultra violet (UV) rays should be limited.
- The use of **LISOZIDE** may also need to be carefully reconsidered in patients who have had previous skin cancer.
- Concomitant use of fluoroquinolones with ACE inhibitors, such as **LISOZIDE**, may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see **CONTRAINDICATIONS**). Renal function should be assessed before initiating treatment, and monitored during concomitant treatment with **LISOZIDE** and fluoroquinolones.

Special precautions:

Hypotension and Electrolyte/Fluid Imbalance

Symptomatic hypotension may occur in the patients with the following: fluid or electrolyte imbalance, e.g. volume depletion, hyponatraemia, hypochloraemic alkalosis, hypomagnesaemia or hypokalaemia which may occur from prior treatment with diuretics, a salt restricted diet, dialysis, or after severe diarrhoea and repeated vomiting.

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. Special consideration should be given when **LISOZIDE** is administered to patients with ischemic 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 % saline. A transient hypotensive response does not warrant discontinuation of further doses.

Once effective blood volume and pressure have been stabilised, therapy at a reduced dosage may be reinstituted; or alternatively either of the components may be used appropriately as mono therapy.

Renal Insufficiency

Thiazides may not be suitable diuretics for use in patients with renal impairment and are ineffective at creatinine clearance values of 30 ml/min or below (i.e. moderate or severe renal insufficiency.)

LISOZIDE 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 **LISOZIDE.**

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, usually 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. If this occurs during therapy with, it should be discontinued. Reinstitution of therapy at a reduced dosage may be possible: or either of the components may be used alone as appropriate.

Haemodialysis

The use of **LISOZIDE** 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) and concurrent treatment with **LISOZIDE.** Consideration to the use of a different type of dialysis membrane or a different class of antihypertensive agent should be given in these patients.

Hepatic Disease

Caution should be exercised when thiazides are 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.

Surgery/Anaesthesia

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

Metabolic and Endocrine Effects

Thiazide diuretics may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required.

Decreased urinary calcium excretion caused by thiazides may result in intermittent and a slightly raised serum calcium concentration. Should marked hypercalcaemia occur, it may be evidence of underlying hyperparathyroidism. **LISOZIDE** therapy should be discontinued before carrying out tests for parathyroid function (see INTERACTIONS). Increased cholesterol and triglyceride levels may be a result of thiazide diuretic therapy.

Thiazide diuretics 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 **LISOZIDE** which contains both components.

Sensitivity/Angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients with angiotensin-converting enzyme inhibitors, including lisinopril. In such cases **LISOZIDE** 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 usually resolves without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate emergency therapy should be administered promptly. This may include the administration of 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 LISOZIDE again.**

Patients with a history of angioedema unrelated to **LISOZIDE** therapy may be at increased risk of angioedema while receiving **LISOZIDE** (see CONTRAINDICATIONS).

In patients receiving thiazides, sensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

Race

LISOZIDE causes a higher rate of angioedema in black patients than in non-black patients.

Desensitisation

Patients receiving ACE-inhibitors during desensitisation treatment (e.g. hymenoptera venom) have sustained anaphylactoid reactions. These reactions have been avoided when ACE-inhibitors were temporarily withheld but they reappeared upon inadvertent rechallenge.

Cough

A non-productive, persistent cough has been reported with the use of ACE-inhibitors. The cough resolves after discontinuation of therapy. ACE-inhibitor-induced cough should be considered as part of the differential diagnoses of cough.

Effects on ability to drive and use machines

LISOZIDE 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 effects depends on the individual's susceptibility. However, when driving vehicles or operating machinery it must be borne in mind that dizziness or tiredness may occur.

INTERACTIONS

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

The decrease in potassium caused by thiazide diuretics is usually attenuated by the effect of lisinopril. The use of potassium supplements, potassium-sparing [~~agents~~] diuretics (such as spironolactone, triamterene, amiloride) or potassium-containing salt substitutes, especially in patients with impaired renal function, may result in a significant increase in serum potassium. Caution should be exercised, when administering **LISOZIDE** concomitantly with any of these medicines and serum potassium should be monitored on a regulator basis.

Lithium

Concomitant administration with **LISOZIDE** may lead to toxic blood concentrations of lithium (see CONTRAINDICATIONS).

Non-steroidal anti-inflammatory drugs (NSAIDs)

Indomethacin may decrease the antihypertensive efficacy of **LISOZIDE.** In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs (NSAIDs), the co-administration of lisinopril may result in a further deterioration in renal function.

The administration of a non-steroidal anti-inflammatory drug can reduce the diuretic, natriuretic and antihypertensive effects of diuretics in some patients.

Tubocurorine

Thiazides may increase the responsiveness to tubocurarine.

Other Antihypertensive Agents

Additive effects may occur with the concomitant administration of **LISOZIDE** with antihypertensive agents.

Alcohol, barbiturates or narcotics

Potentiation of orthostatic hypotension caused by thiazides may occur with the concomitant administration of **LISOZIDE** with antihypertensive agents.

Antidiabetics

Dosage adjustment of the antidiabetic medicine may be required with the concomitant use with **LISOZIDE**.

Corticosteroids, corticotropin (ACTH)

Concomitant use with **LISOZIDE** may intensify electrolyte depletion and hypokalaemia.

Pressor amines (e.g. adrenalin)

LISOZIDE may decrease response to pressor amines. This decrease in response is not sufficient to prelude the use of pressor amines.

Aliskiren-containing products

The concomitant use of **LISOZIDE** with aliskiren-containing products is contraindicated (see CONTRAINDICATIONS).

Fluoroquinolones

Concomitant use of fluoroquinolones and ACE inhibitors, such as **LISOZIDE**, may precipitate acute kidney injury (see CONTRAINDICATIONS).

HUMAN REPRODUCTION

Safety in pregnancy and lactation has not been established (see WARNINGS). **LISOZIDE** can cause foetal and neonatal morbidity and mortality when administered to pregnant women

during the 2nd and 3rd trimesters. **LISOZIDE** passes through the placenta and can be presumed to cause disturbance in foetal blood regulatory mechanisms.

Use of **LISOZIDE** during the second and third trimester has been associated with foetal and neonatal injury including hypotension, renal failure, hyperkalaemia, oliguria, anuria and skull hypoplasia in the newborn. Maternal oligohydramnios, presumably representing decreased foetal renal function, has occurred and may result in limb contractures, craniofacial deformations and hypoplastic lung development. Prematurity and low birth mass can occur. These adverse effects to the embryo and foetus do not appear to have resulted from intrauterine ACE-inhibitor exposure limited to the first trimester.

Infants whose mothers have taken **LISOZIDE** should be closely observed for hypotension, oliguria and hyperkalaemia. Lisinopril, which crosses the placenta, has been removed from the neonatal circulation by peritoneal dialysis with some clinical benefit. There is no experience with the removal of hydrochlorothiazide, which also crosses the placenta, from the neonatal circulation.

The routine use of diuretics in otherwise healthy pregnant woman is not recommended and exposes mother and foetus to unnecessary hazard. Diuretics do not prevent development of toxaemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxaemia. Thiazides cross the placental barrier and appear in cord blood. Hazards include foetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which occur in the adult.

Lactation

It is not known whether lisinopril is distributed into human breast milk; however the thiazides do appear in human milk. If **LISOZIDE** is deemed essential, the patient should stop nursing.

DOSAGE AND DIRECTIONS FOR USE

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 to 4 weeks with

this dosage, the dosage may be increased to a maximum of two tablets, administered once daily.

Prior Diuretic therapy

Symptomatic hypotension may occur after the initial dose of **LISOZIDE;** this phenomenon occurs more likely 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 **LISOZIDE;** or if this is not possible, lisinopril should be given alone at a low initial dose of 5 mg.

Renal impairment

Thiazides may not be suitable diuretics for use in patients with renal impairment and are ineffective in moderate or severe renal impairment (creatinine clearance values of 30 ml/min or below).

LISOZIDE should not be used as initial therapy in any patient with renal insufficiency.

In patients with creatinine clearance of >30 and <80 ml/min, **LISOZIDE** may be used, but only after titration of the individual components.

Use in children

Safety and efficacy in children have not been established.

Use in the elderly

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

SIDE-EFFECTS

The following side effects have been observed and reported during treatment with **LISOZIDE** with the following frequencies: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon

(≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), unknown (cannot be estimated from the available data).

The side-effects below are classified by system organ class and frequency according to the following convention:

very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000); unknown.

The following side effects have been reported for lisinopril

System organ class	Side effect	Frequency
Blood and lymphatic system disorders	Decreases in haemoglobin, decreases in haematocrit	rare
	Bone marrow depression, anaemia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis, haemolytic anaemia, lymphadenopathy, autoimmune disease	very rare
Immune system disorders	Anaphylactic/anaphylactoid reaction	unknown
Endocrine disorders	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	rare
Metabolism and nutrition disorders	Hypoglycaemia	very rare
Cardiac disorders	Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients, palpitations, tachycardia, Raynaud's syndrome	uncommon
Hepatobiliary disorders	Elevated liver enzymes and bilirubin	uncommon
	Hepatitis – either hepatocellular or cholestatic, jaundice and hepatic failure*	very rare

Nervous system disorders	Dizziness, headache, syncope.	common
	Paraesthesia, vertigo, taste disturbance,	uncommon
	Olfactory disturbance	rare
Psychiatric disorders	sleep disturbances, mood alterations, depressive symptoms	uncommon
	Mental confusion	rare
Renal and urinary disorders	Renal dysfunction	common
	Uraemia, acute renal failure	rare
	Oliguria/anuria	very rare
General disorders and administration site conditions	Asthenia, fatigue	uncommon
Reproductive system and breast disorders	Impotence	uncommon
	Gynaecomastia	rare
Respiratory, thoracic and mediastinal disorders	Cough	common
	Rhinitis	uncommon
	Bronchospasm, sinusitis, allergic alveolitis/eosinophilic pneumonia	very rare
Gastrointestinal disorders	Diarrhoea, vomiting	common
	Nausea, abdominal pain and indigestion	uncommon
	Dry mouth	rare
	Pancreatitis, intestinal angioedema	very rare
Skin and subcutaneous tissue disorders	Rash, pruritus	uncommon
	Hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx, urticaria, alopecia, psoriasis	rare
	Diaphoresis, pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema	very rare

	multiforme, cutaneous pseudolymphoma.**	
Vascular disorders	Orthostatic effects (including orthostatic hypotension)	common
	Flushing	unknown
Investigations	Increases in blood urea, increases in serum creatinine, hyperkalaemia	uncommon
	Hyponatraemia	rare

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

The following side effects have been reported for hydrochlorothiazide

System organ class	**Side effect**	**Frequency**
Infections and infestations	Sialadenitis	Unknown
Blood and lymphatic system disorders	Leucopenia, neutropenia/agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, bone marrow depression	Unknown
Metabolism and nutrition disorders	Anorexia, hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance (including hyponatraemia, hypokalaemia, hypochloremic alkalosis and hypomagnesaemia), increases in cholesterol and triglycerides, gout	Unknown
Psychiatric disorders	Restlessness, depression, sleep disturbance	Unknown
Nervous system disorders	Loss of appetite, paraesthesia, light-headedness	Unknown
Eye disorders	Xanthopsia, transient blurred vision, acute myopia and acute angle-closure glaucoma	Unknown
Ear and labyrinth disorders	Vertigo	Unknown

Cardiac disorders	Postural hypotension	Unknown
Vascular disorders	Necrotising angiitis (vasculitis, cutaneous vasculitis)	Unknown
Respiratory, thoracic and mediastinal disorders	Respiratory distress (including pneumonitis and pulmonary oedema)	Unknown
Gastrointestinal disorders	Gastric irritation, diarrhoea, constipation, pancreatitis	Unknown
Hepato-biliary disorders	Jaundice (intrahepatic cholestatic jaundice)	Unknown
Skin and subcutaneous tissue disorders	Photosensitivity reactions, rash, systemic lupus erythematosus, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, urticaria, anaphylactic reactions, toxic epidermal necrolysis	Unknown
Musculoskeletal and connective tissue disorders	Muscle spasm, muscle weakness	Unknown
Renal and urinary disorders	Renal dysfunction, interstitial nephritits	Unknown
General disorders and administration site conditions	Fever, weakness	Unknown

KNOWN SYMPTOMS OF OVER-DOSAGE AND PARTICULARS OF ITS TREATMENTS

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

Lisinopril: The most likely features of overdosage may include hypotension, electrolyte disturbance and renal failure. Treatment is symptomatic and supportive.

Hydrochlorothiazide: The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digitalis has been used concomitantly, hypokalaemia may accentuate cardiac arrhythmias.

IDENTIFICATION

LISOZIDE-10:

Light pink, circular, biconvex, uncoated tablets.

LISOZIDE-20:

White to off white, circular, biconvex, uncoated tablets.

PRESENTATION

LISOZIDE-10:

Blister pack (Clear PVDC coated PVC film and Aluminium foil) of 3 x 10 tablets.

LISOZIDE-20:

Blister pack (Clear PVDC coated PVC film and Aluminium foil) of 3 x 10 tablets.

Not all pack sizes may be marketed.

STORAGE INSTRUCTIONS

Store in a dry place at or below 25 °C. Protect from light.

Keep blister packs in the carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

LISOZIDE–10: A39/7.1.3/0108

LISOZIDE–20: A39/7.1.3/0109

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