

SCHEDULING STATUS:

S3

PROPRIETARY NAME AND DOSAGE FORM:

LISORETIC 10/12,5 tablets

LISORETIC 20/12,5 tablets

COMPOSITION:

LISORETIC 10/12,5: Each tablet contains 10 mg lisinopril (as the dihydrate) and 12,5 mg hydrochlorothiazide.

LISORETIC 20/12,5: Each tablet contains 20 mg lisinopril (as the dihydrate) and 12,5 mg hydrochlorothiazide.

PHARMACOLOGICAL CLASSIFICATION:

A 7.1.3 Other hypotensives.

PHARMACOLOGICAL ACTION:

LISORETIC 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, play 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.

Pharmacokinetics

The concomitant administration of lisinopril and hydrochlorothiazide has no clinical 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 gastrointestinal 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.

CONTRA-INDICATIONS:

- Anuria.
- Hypersensitivity to any component of this product.
- Patients with a history of angioedema relating to previous treatment with an angiotensin-converting enzyme inhibitor.
- Patients with hereditary or idiopathic angioedema (see Special Precautions).
- Hypersensitivity to other sulphonamide-derived medicines.
- Pregnancy and Nursing Mothers – see Pregnancy and Lactation.
- Patients with aortic stenosis or hypertrophic cardiomyopathy.

WARNINGS

Pregnancy:

Should a woman become pregnant while receiving an ACE-inhibitor, the treatment must be stopped immediately and switched to an alternative medicine. Should a woman contemplate pregnancy, the doctor should institute alternative medication.

ACE-inhibitors can cause foetal and neonatal morbidity and mortality when administered to pregnant women during the 2nd and 3rd trimesters. ACE-inhibitors pass through the placenta and can be presumed to cause disturbance in foetal blood regulatory mechanisms.

Use of ACE inhibitors 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 **LISORETIC** 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 toxæmia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxæmia. 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.

Breast-feeding

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

INTERACTIONS

- *Serum Potassium*

The decrease in potassium caused by thiazide diuretics is usually potentiated 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. Should it be required to administer **LISORETIC** concomitantly with any of these agents, caution should be exercised and serum potassium should be monitored on a regular basis.

- *Lithium*

The concomitant use of lithium with diuretics or ACE-inhibitors is not indicated. The renal clearance of lithium is reduced by ACE-inhibitors and diuretic agents and a high risk of lithium toxicity exists. The prescribing information for lithium preparation should be reviewed before use of these preparations.

- *Non-steroidal anti-inflammatory drugs (NSAIDs)*

Indomethacin may decrease the antihypertensive efficacy of **LISORETIC**. 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 agent can reduce the diuretic, natriuretic and antihypertensive effects of diuretics in some patients.

- *Tubocurarine*

Thiazides may increase the responsiveness to tubocurarine.

- *Other Antihypertensive Agents*

Additive effects may occur.

- *Alcohol, barbiturates or narcotics*

Potential of orthostatic hypotension caused by thiazides may occur.

- *Antidiabetic medicine* (oral agents and insulin)

Dosage adjustment of the antidiabetic medicine may be required with the concomitant use of a thiazide diuretic.

- *Corticosteroids, ACTH*

Concomitant use of a thiazide diuretic may intensify electrolyte depletion and hypokalaemia.

- *Pressor Amines* (e.g. adrenalin):

Thiazide diuretics may decrease response to pressor amines. This decrease in response is not sufficient to preclude the use of pressor amines.

PREGNANCY AND LACTATION

Safety in pregnancy and lactation has not been established. Refer to WARNINGS

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 Treatment with Diuretics

Symptomatic hypotension may occur after the initial dose of **LISORETIC**; 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 **LISORETIC**, 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.)

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 children

Safety and efficacy in children have not been established.

Use in the Elderly

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

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-effects

The following side effects are listed according to the organ class system for **LISORETIC** as well as for the individual components, lisinopril and hydrochlorothiazide.

Gastrointestinal

Lisoretic

Less frequently: diarrhoea

Rare: nausea, vomiting

Hydrochlorothiazide

Less frequently: gastric irritation, constipation

Lisinopril

Rare: abdominal pain and indigestion

Nervous system

Lisoretic

Frequently: headache, dry mouth

Less frequently: dizziness and fatigue, which generally diminish when the dosages are reduced

Rare: paraesthesia, Asthenia

Hydrochlorothiazide: vertigo, fever

Frequently: restlessness

Lisinopril: vertigo, sleep disturbance, hypoaesthesia

Rare: paraesthesia

Psychiatric

Lisinopril: mood alterations, mental confusion

Musculoskeletal

Lisoretic

Frequently: muscle cramps

Rare: weakness

Hydrochlorothiazide

Frequently: muscle spasm

Hepato-biliary

Hydrochlorothiazide: hyperglycaemia, glycosuria

Rare: jaundice (intrahepatic cholestatic jaundice), pancreatitis, hyperuricaemia

Lisinopril: hepatitis (hepatocellular or cholestatic)

Respiratory

Lisoretic

Frequently: dry cough

Hydrochlorothiazide: respiratory distress including pneumonitis and pulmonary oedema, anaphylactic reactions.

Lisinopril: bronchospasm, rhinitis, sinusitis, pulmonary infiltrates

Cardiac

Lisoretic

Rare: palpitation, chest discomfort

Lisinopril

Rare: myocardial infarction or cerebrovascular accident possibly secondary to excessive hypotension in high risk patients (see Special Precautions), tachycardia

Vascular

Lisoretic

Less frequently: hypotension including orthostatic hypotension.

Hydrochlorothiazide: necrotizing angiitis (vasculitis) (cutaneous vasculitis)

Renal and urinary

Hydrochlorothiazide

Rare: renal failure, renal dysfunction and interstitial nephritis.

Lisinopril: diaphoresis, uraemia, oliguria/anuria, renal dysfunction, acute renal failure

Skin and appendages

Lisoretic

Less frequently: rash

Rare: photosensitivity

Hydrochlorothiazide: purpura

Less frequently: photosensitivity

Rare: urticaria

Lisinopril: psoriasis and severe skin disorders, including pemphigus, toxic epidermal necrolysis, erythema multiforme, alopecia

Less frequently: pruritus

Rare: urticaria

Blood and lymphatic system

Hydrochlorothiazide: leucopenia, aplastic anaemia, haemolytic anaemia

Rare: agranulocytosis, thrombocytopenia

Lisinopril

Less frequently: haemolytic anaemia

Eye

Hydrochlorothiazide: xanthopsia, transient blurred vision

Metabolism and nutrition

Lisoretic

Rare: gout

Hydrochlorothiazide

Frequently: electrolyte imbalance including hyponatraemia

Less frequently: anorexia

Lisinopril: taste disturbances, hyponatraemia

Endocrine

Hydrochlorothiazide: sialoadenitis

Reproductive system

Lisoretic

Less frequently: impotence

Hypersensitivity Reactions

Lisoretic

Rare: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported (see Contra-Indications & Special Precautions). A symptom complex has been reported which may include fever, vasculitis, myalgia, arthralgia/arthritis, a positive Antinuclear antibody (ANA), elevated erythrocyte sedimentation rate, eosinophilia and leukocytosis.

Lisinopril: Stevens-Johnson Syndrome

Laboratory Test Findings

Lisoretic

Hyperkalaemia, hyperglycaemia and hyperuricaemia and have been noted. Increases in serum creatinine and in blood urea nitrogen have been reported in patients without renal impairment. These are usually reversible if medication is discontinued.

Bone marrow depression manifesting as anaemia and/or thrombocytopenia and/or leucopenia have also occurred. Agranulocytosis has been reported.

Small decreases in hemoglobin and haematocrit have been reported frequently in hypertensive patients treated with **LISORETIC** but were rarely of clinical significance unless another cause of anaemia was also present.

Elevations of liver enzymes (AST and ALT) and/or serum bilirubin have been reported.

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, hypochloremic 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 this medication 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 reinstated; 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.)

LISORETIC should not be administered to patients with a creatinine clearance \leq 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, 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 **LISORETIC**, 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 **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 concurrent treatment with an ACE-inhibitor. 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. **LISORETIC** 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 **LISORETIC** 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 **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 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 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 (see also Contra-indications).

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

LISORETIC 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 diagnose of cough.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Treatment is symptomatic and supportive. No specific information is available on the treatment of overdose with **LISORETIC**. Therapy with **LISORETIC** 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 overdose 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:

LISORETIC 10/12,5 : A peach coloured, round, uncoated, 6 mm biconvex tablet., marked 'LH'.

LISORETIC 20/12,5 : A white coloured, round, uncoated, 8 mm biconvex scored tablet., marked "LH".

PRESENTATION:

PVC/PVDC Aluminium blister packs of 30 tablets.

STORAGE INSTRUCTIONS:

Store below 25°C. Protect from light.

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

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

LISORETIC 10/12,5 : 37/7.1.3/0475

LISORETIC 20/12,5 : 37/7.1.3/0476

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

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SKEDULERINGSSTATUS:

S3

EIENDOMSNAAM EN DOSEERVORM:

LISORETIC 10/12,5 tablette

LISORETIC 20/12,5 tablette

SAMESTELLING:

LISORETIC 10/12,5: Elke tablet bevat 10 mg lisinopriël (as die dihidraat) en 12,5 mg hidrochloortiasied.

LISORETIC 20/12,5: Elke tablet bevat 20 mg lisinopriël (as die dihidraat) en 12,5 mg hidrochloortiasied.

FARMAKOLOGIESE KLASSIFISERING:

A.7.1.3 Ander hipotensiewe middels.

FARMAKOLOGIESE WERKING

LISORETIC is 'n kombinasie van 'n angiotensienomsettingsensiem-inhibeerder, lisinopriël en 'n diuretikum, hidrochloortiasied. Beide hierdie komponente is wyd op hul eie en in kombinasie gebruik vir die behandeling van hipertensie as gevolg van additiewe uitwerkings.

Lisinopriël is 'n peptidiedipeptidase-inhibeerder en inhibeer die angiotensienomsettingsensiem(AOE) wat die omsetting van angiotensien I na angiotensien II kataliseer.

Angiotensien II is 'n vatvernouende peptied wat ook aldosteroonafskeiding deur die adrenale korteks stimuleer.

Inhibisie van AOE veroorsaak verminderde konsentrasies van angiotensien II wat weer verminderde vasopressoraktiwiteit en verminderde aldosteroonafskeiding veroorsaak. Verminderde aldosteroonafskeiding mag 'n verhoging in serumkaliumkonsentrasie veroorsaak.

Die meganisme van werking waardeur lisinopriël bloeddruk verlaag, is hoofsaaklik deur onderdrukking van die renien-angiotensien-aldosteroonsisteem; lisinopriël het egter ook antihipertensiewe uitwerkings in pasiënte met lae-renien-hipertensie.

AOE is identies aan kininase II, 'n ensiem wat bradikiniën afbreek. Dit is moontlik dat verhoogde vlakke van bradikiniën, 'n kragtige vasodilasie peptied, 'n rol mag speel in die terapeutiese uitwerking van lisinopriël. Dit moet egter nog opgeklaar word.

Hidrochloortiasied is 'n tiasied-diuretikum en 'n antihipertensiewe middel. Dit beïnvloed die distale nierbuisie-meganisme van elektrolietherabsorpsie en verhoog uitskeiding van natrium en chloried in ongeveer ekwivalente hoeveelhede. Natriuresis mag deur 'n sekere mate van verlies aan kalium en bikarbonaat vergesel word. Die meganisme van die antihipertensiewe uitwerking van die tiasiede is onbekend. Tiasiede het gewoonlik geen invloed op normale bloeddruk nie.

Farmakokinetika

Die gelyktydige toediening van lisinopriël en hidrochloortiasied het geen kliniese beduidende uitwerking op die farmakokinetika van beide geneesmiddels nie.

Lisinopriël

Ongeveer 60% van lisinopriël word na orale toediening geabsorbeer. Die absorpsie wissel tussen individue (6 tot 60%).

Na orale toediening van lisinopriël word piek serumkonsentrasies binne ongeveer 7 uur bereik. Lisinopriël het 'n effektiewe halfleeftyd van 12 uur. Lisinopriël bind nie aan ander serumproteïene nie.

Die absorpsie van lisinopriël word nie deur die teenwoordigheid van voedsel in die spysverteringskanaal beïnvloed nie.

Lisinopriël word nie gemetaboliseer nie en al die geabsorbeerde geneesmiddel word onveranderd in die urine uitgeskei. Ingekorte nierfunksie verminder eliminasië van lisinopriël. Hierdie vermindering word alleenlik klinies belangrik wanneer die glomerulêre filtrasiëtempo tot onder 30 ml/min daal. Lisinopriël kan deur dialise verwyder word.

Ouer pasiënte het hoër bloeddrukke en hoër waardes vir die area onder die plasmakonsentrasie-tydkurve as jonger pasiënte.

Hidrochloortiasied

Die plasma halfleeftyd van hidrochloortiasied kan tussen 5 en 15 uur wissel. Ongeveer 60% van die dosis word binne 24 uur onveranderd uitgeskei. Na orale toediening van hidrochloortiasied begin diuresis binne 2 uur, piek vlakke word na ongeveer 4 uur bereik

en duur vir 6 tot 12 uur voort.

INDIKASIES

Ligte tot matige hipertensie in pasiënte wat gestabiliseer is op die individuele komponente wat teen dieselfde verhoudings toegedien is.

KONTRA-INDIKASIES

- Anurie.
- Hipersensitiwiteit teenoor enige bestanddeel van hierdie produk.
- Pasiënte met 'n geskiedenis van angio-edeem verwant aan vorige behandeling met 'n angiotensienomsettingsensiem-inhibeerder.
- Pasiënte met aangebore of idiopatiese angio-edeem (sien Spesiale Voorsorgmaatreëls).
- Hipersensitiwiteit teenoor ander sulfonamied-afgeleide medisyne.
- Swangerskap en Borsvoedende Moeders - sien Swangerskap en Laktasie.
- Pasiënte met stenose van die aorta of hipertrofiese kardiomiopatie.

WAARSKUWINGS

Swangerskap:

Indien 'n vrou sou swanger word terwyl sy 'n AOE-inhibeerder ontvang, moet die behandeling onmiddellik gestaak word en na 'n alternatiewe medisyne verander word. Indien 'n vrou swangerskap sou oorweeg, moet die geneesheer alternatiewe medikasie instel.

AOE-inhibeerders kan fetale en neonatale morbiditeit en mortaliteit veroorsaak as dit aan swanger vrouens tydens die 2de en 3de semester toegedien word. AOE-inhibeerders beweeg oor die plasenta en daar kan aanvaar word dat dit versteurings in fetale bloedbeheermeganismes veroorsaak.

Gebruik van AOE-inhibeerders tydens die tweede en derde trimester is met fetale en neonatale besering, insluitend hipotensie, nierversaking, hiperkalemie, oligurie, anurie en skedel hipoplasie in die pasgeborene, geassosieer. Oligohidramnios van die moeder, wat waarskynlik verminderde fetale nierfunksie verteenwoordig, het voorgekom en mag kontraktuur van ledemate, wanvorming van die skedel en gesig, en hipoplastiese longontwikkeling veroorsaak. Prematuriteit en lae massa by geboorte kan voorkom. Dit wil voorkom dat hierdie nadelige uitwerkinge ten opsigte van die embryo en fetus nie deur

blootstelling aan 'n AOE-inhibeerder in die baarmoeder wat tot die eerste trimester beperk is, veroorsaak word nie.

Suigelinge van moeders wat **LISORETIC** geneem het, moet versigtig vir hipotensie, oligurie en hiperkalsemie dopgehou word. Lisinopriël wat die plasenta oorsteek, is van die neonatale sirkulasie met 'n mate van kliniese voordeel deur peritoneale dialise verwyder. Daar bestaan geen ondervinding met die verwydering van hidrochloortiasied, wat ook oor die plasenta beweeg, uit die neonatale bloedsomloop nie.

Die roetine gebruik van diuretika in andersins gesonde swanger vrouens word nie aanbeveel nie en stel die moeder en fetus aan onnodige gevare bloot. Diuretika verhoed nie die ontwikkeling van toksemie van swangerskap en daar is geen bevredigende bewyse dat hulle vir die behandeling van toksemie nuttig is nie. Tiasiede beweeg oor die skans van die plasenta en word in koordbloed aangetref. Gevare sluit in fetale of neonatale geelsug, trombositopenie en moontlik ook ander nadelige reaksies wat by volwassenes voorkom.

Borsvoeding

Dit is nie bekend of lisinopriël in menslike borsmelk versprei word nie; tiasiede word egter in menslike melk aangetref. Indien die geneesmiddel as essensieel beskou word, moet die pasiënt borsvoeding staak.

INTERAKSIES

- *Serumkalium*

Die vermindering in kalium veroorsaak deur tiasied-diuretika word gewoonlik deur die uitwerking van lisinopriël versterk. Die gebruik van kaliumsupplemente, kaliumsparende middels of kalium-bevattende soutvervangers, veral in pasiënte met ingekorte nierfunksie, mag 'n beduidende verhoging in serumkalium veroorsaak. Indien dit nodig is om **LISORETIC** saam met enigeen van hierdie middels toe te dien, moet omsigtigheid uitgeoefen en serumkalium gereeld gemoniteer word.

- *Litium*

Die gelyktydige gebruik van litium saam met diuretika of AOE-inhibeerders word nie aangedui nie. Nieropruiming van litium word deur AOE-inhibeerders en diuretika verminder en daar bestaan 'n hoë risiko van litiumtoksisiteit. Die inligting vir die voorskryf van litiumpreparate moet nagegaan word voordat hierdie preparate gebruik word.

- *Nie-steroïedale anti-inflammatoriese middels (NSAIMs)*

Indometasien mag die antihipertensiewe doeltreffendheid van **LISORETIC** verminder. In sommige pasiënte met gekompromitteerde nierfunksie wat met nie-steroïedale anti-inflammatoriese middels (NSAIMs) behandel word, mag die gelyktydige toediening van lisinopriël addisionele verslegting van nierfunksie veroorsaak.

Die toediening van 'n nie-steroïedale anti-inflammatoriese middel kan die diuretiese, natriuretiese en antihipertensiewe uitwerkings van diuretika in sommige pasiënte verminder.

- *Tubokurarien*

Tiasiede mag die reaksie op tubokurarien verhoog.

- *Ander Antihipertensiewe Middels*

Additiewe uitwerkings mag voorkom.

- *Alkohol, barbiturate of dwelmmiddels*

Potensiëring van ortostatiese hipotensie veroorsaak deur tiasiede mag voorkom.

- *Antidiabetiese medisyne (orale middels en insulien)*

Dosisaanpassing van die antidiabetiese medisyne mag nodig wees wanneer 'n tiasied-diuretikum gelyktydige gebruik word.

- *Kortikosteroïede, ACTH*

Gelyktydige gebruik van 'n tiasied-diuretikum mag elektrolietuitputting en hipokalemie vererger.

- *Pressoramiene (bv. adrenalien)*

Tiasied-diuretika mag die reaksie op pressoramiene verminder. Hierdie vermindering van die reaksie is nie voldoende om die gebruik van pressoramiene uit te sluit nie.

SWANGERSKAP EN LAKTASIE

Veiligheid in swangerskap en laktasie is nie vasgestel nie. Verwys na WAARSKUWINGS.

DOSERING EN GEBRUIKSAANWYSINGS

Die gewone dosis is een tablet per dag, wat altyd op ongeveer dieselfde tyd van die dag geneem word. As die gewenste kliniese uitwerking nie binne 2 tot 4 weke bereik kan word nie, word dit aanbeveel dat die dosering tot 'n maksimum van twee tablette wat een keer per dag toegedien word, verhoog word.

Voorige Behandeling met Diuretika

Simptomatiesie hipotensie mag na die eerste dosis van **LISORETIC** voorkom; hierdie verskynsel is meer geneig om te gebeur in pasiënte wat ly aan volume- en/of soutuitputting as gevolg van vorige diuretiese behandeling. Indien moontlik, moet die diuretiese terapie vir 2-3 dae voor instelling van terapie met **LISORETIC** gestaak word, of as dit nie moontlik is nie, behoort lisinopriël alleen teen 'n lae aanvangsdosis van 5 mg gegee te word.

Nierinkorting

Tiasiede mag nie geskikte diuretika wees vir gebruik in pasiënte met nierinkorting en is in matige tot ernstige nierinkorting (kreatinienopruimingwaardes van 30 ml/min of laer), nie effektief nie.

LISORETIC behoort nie as aanvangsterapie gebruik te word in enige pasiënt met nierinkorting nie. **LISORETIC** kan in pasiënte met kreatienopruiming van >30 en <80 ml/min gebruik word, maar alleenlik na titrasie van die individuele komponente.

Gebruik in kinders

Veiligheid en doeltreffendheid in kinders is nie vasgestel nie.

Gebruik in Bejaardes

Daar is geen beduidende verskil tussen bejaarde en jonger hipertensiewe pasiënte in die doeltreffendheid en verdraagsaamheid teenoor lisinopriël en hidrochloortiasied wat gelyktydig toegedien word nie.

NEWE-EFFEKTE EN SPESIALE VOORSORGMAATREËLS:

Nuwe-effekte

Die volgende nuwe-effekte word gelys volgens die orgaanklas-sisteem vir **LISORETIC**, asook vir die individuele komponente, lisinopriël en hidrochloortiasied.

Gastroïntestinaal

Lisoretic

Minder frekwent: diarree

Seldsaam: naarheid, braking

Hidrochloortiasied

Minder frekwent: gastriese irritasie, hardlywigheid

Lisinopriël

Seldsaam: abdominale pyn en swak spysvertering

Senusisteem

Lisoretic

Frekwent: hoofpyn, droë mond

Minder frekwent: duiseligheid en moegheid, wat meestal verminder as die doserings verlaag word

Seldsaam: parestesie, astenie

Hidrochloortiasied: vertigo, koors

Frekwent: rusteloosheid

Lisinopriël: vertigo, slaapversteurings, hipoëstesie

Seldsaam: parestesie

Psigiatries

Lisinopriël: veranderings van humeur, geestesverwarring

Muskuloskeletaal

Lisoretic

Frekwent: spierkrampe

Seldsaam: swakheid

Hidrochloortiasied

Frekwent: spierspasma

Hepatobiliêr

Hidrochloortiasied: hiperglisemie, glikosurie

Seldsaam: geelsug (intrahepatiese cholestatiese geelsug), pankreatitis, hiperurisemie

Lisinopriël: hepatitis (hepatosellulêr of cholestasies)

Respiratories

Lisoretic

Frekwent: droë hoes

Hidrochloortiasied: respiratoriese nood, insluitend pneumonitis en pulmonale edeem, anafilaktiese reaksies

Lisinopriël: brongospasma , rinitis, sinusitis, pulmonale infiltrate

Kardiaal

Lisoretic

Seldsaam: hartkloppings, borsongemak

Lisinopriël

Seldsaam: miokardiale infarsie of serebrovaskulêre insident moontlik sekondêr tot oormatige hipotensie in hoë-risiko pasiënte (sien Spesiale Voorsorgmaatreëls), tagikardie

Vaskulêr

Lisoretic

Minder frekwent: hipotensie, insluitend ortostatiese hipotensie.

Hidrochloortiasied: nekrotiserende angeïtis (vaskulitis) (vaskulitis van die vel)

Renaal en urinêr

Hidrochloortiasied:

Seldsaam: nierversaking, nierdisfunksie en interstisiële nefritis.

Lisinopriël: diaforese, uremie, oligurie/anurie, nierdisfunksie, akute nierversaking.

Vel en aanhangsels

Lisoretic

Minder frekwent: veluitslag

Seldsaam: fotosensitiwiteit

Hidrochloortiasied: purpura

Minder frekwent: fotosensitiwiteit

Seldsaam: urtikarie

Lisinopriël: psoriase en ernstige velsiektes, insluitend pemfigus, toksiese

epidermale nekrolise, erythema multiforme, alopesie

Minder frekwent: pruritus

Seldsaam: urtikarie

Bloed en limfatiese sisteem

Hidrochloortiasied: leukopenie, aplastiese anemie, hemolitiese anemie

Seldsaam: agranulositose, trombositopenie

Lisinopriël:

Minder frekwent: hemolitiese anemie

Oog

Hidrochloortiasied: xantopsie, verbygaande versteurde visie

Metabolisme en voeding

Lisoretic:

Seldsaam: jig

Hidrochloortiasied:

Frekwent: elektrolietwanbalans, insluitend hiponatremie

Minder frekwent: anoreksie

Lisinopriël: smaakversteurings, hiponatremie

Endokrien

Hidrochloortiasied: sialadenitis

Voortplantingsisteem

Lisoretic

Minder frekwent: impotensie

Hipersensitiwiteitsreaksies

Lisoretic

Seldsaam: Angio-edeem van die gesig, ekstremitate, lippe, tong, glottis en/of larinks is aangemeld (sien Kontra-indikasies en Spesiale Voorsorgmaatreëls). 'n Simptoomkompleks is aangemeld wat koors, vaskulitis, mialgie, artralgie/artritis, 'n positiewe Anti-nukleêre teenliggaampie (ANA), verhoogde eritrosiet sedimentasietempo, eosinofilie en leukositose mag insluit.

Lisinopriël: Stevens-Johnson Sindroom

Laboratoriumtoetsbevindings

Lisoretic

Hiperkalemie, hiperglisemie en hiperurisemie is aangemeld. Verhogings in serumkreatinien en in bloedureumstikstof is aangemeld in pasiënte sonder nierinkorting. Hierdie simptome is gewoonlik omkeerbaar as die medikasie gestaak word.

Beenmurgonderdrukking wat manifesteer as anemie en/of trombositopenie en/of leukopenie het ook voorgekom. Agranulositose is gerapporteer.

Klein verlagings in hemoglobien en hematokrit is dikwels aangemeld in hipertensiewe pasiënte wat met **LISORETIC** behandel is, maar tensy ander oorsake van anemie ook teenwoordig was, was dit selde van kliniese betekenis.

Verhogings van lewerensieme (AST en ALT) en/of serumbilirubien is aangemeld.

Spesiale Voorsorgmaatreëls:

Hipotensie en Elektroliet-/Vloeistofwanbalans

Simptomatiese hipotensie mag voorkom in pasiënte met die volgende: vloeistof- of elektrolietwanbalans, bv. volume-uitputting, hiponatremie, hipochloremiese alkalose, hipomagnesemie, of hipokalemie wat mag voorkom as gevolg van vorige behandeling met diuretika, 'n soutbeperkte dieet, dialise, of na ernstige diarree en herhaalde braking. Bepaling van serumelektroliete moet met geskikte tussenposes in sulke pasiënte uitgevoer word.

In pasiënte met 'n verhoogde risiko van simptomatiese hipotensie behoort die begin van behandeling en dosisaanpassing onder noukeurige mediese toesig gemoniteer te word. Spesiale aandag behoort gegee te word wanneer hierdie medikasie aan pasiënte met iskemiese hart- of serebrovaskulêre siekte toegedien word omdat 'n buitensporige verlaging in bloeddruk miokardiale infarksie of serebrovaskulêre insidente mag veroorsaak.

Indien hipotensie voorkom, behoort die pasiënt op die naat van sy/haar rug geplaas te word en, indien nodig, behoort 'n intraveneuse infusie van 0,9% soutoplossing toegedien te word. 'n Verbygaande hipotensiewe reaksie noodsaak nie staking van daaropvolgende dosisse nie.

Sodra effektiewe bloedvolume en -druk gestabiliseer is, kan terapie teen 'n verminderde dosering weer ingestel word; of as alternatief kan iedereen van die komponente toepaslik

as monoterapie gebruik word.

Nierontoereikendheid

Tiasiede mag nie geskikte diuretika wees vir gebruik in pasiënte met nierinkorting, en by kreatinienopruimingwaardes van 30 ml/min of laer (d.i. matige tot ernstige nierontoereikendheid), is dit nie effektief nie.

LISORETIC behoort nie aan pasiënte met 'n kreatinienopruiming \leq 80 ml/min toegedien te word, totdat titrasie van die individuele komponente die noodsaaklikheid vir die dosisse wat in **LISORETIC** teenwoordig is, aangetoon het nie.

In sommige pasiënte met bilaterale stenose van die renale arterie of stenose van die arterie wat 'n enkele nier voorsien, wat AOE-inhibeerderterapie ontvang het, is verhogings in bloedureum en serumkreatinien waargeneem wat gewoonlik na staking van terapie omkeerbaar was. Dit sal veral in pasiënte met nierontoereikendheid voorkom. Sommige hipertensiewe pasiënte met geen duidelike vooraf-bestaande niersiekte het verhogings in bloedureum en serumkreatinien ontwikkel toe lisinopriël saam met 'n diuretikum toegedien is. Indien dit tydens terapie met **LISORETIC** voorkom, behoort dit gestaak te word. Hervatting van terapie teen 'n verminderde dosering mag moontlik wees; of iedereen van die komponente mag soos toepaslik alleen gebruik word.

Hemodialise

Die gebruik van **LISORETIC** is nie aangedui in pasiënte wat dialise vir nierversaking benodig nie. Anafilaktoïed reaksies is aangemeld in pasiënte wat hemodialise prosedures met sekere dialise membrane (bv. met hoë-vloei membrane AN 69) en gelyktydige behandeling met 'n AOE-inhibeerder, ondergaan. Daar moet oorweging geskenk word om 'n ander soort dialise membraan te gebruik, of 'n ander klas van antihypertensiewe middel behoort aan hierdie pasiënte gegee te word.

Hepatiëse Siekte

Omsigtigheid moet uitgeoefen word wanneer tiasiede in pasiënte met hepatiëse inkorting of progressiewe lewersiekte gebruik word, omdat klein veranderings in vloeistof- en elektrolietbalans hepatiëse koma in hierdie pasiënte mag presipiteer.

Chirurgie/Narkose

In pasiënte wat groot operasies ondergaan of tydens narkose met middels wat hipotensie veroorsaak, mag lisinopriël angiotensien II formasie sekondêr tot kompensatoriese

vrystelling van renien blokkeer. Indien hipotensie sou voorkom en daar geglo word dat dit deur hierdie meganisme veroorsaak word, kan dit met volume-uitsetting gekorrigeer word.

Metaboliëse en Endokriene Uitwerkings

Tiasied-diuretika mag glukosetoleransie inkort. Dosisaanpassing van antidiabetiese middels, insluitend insulien, mag nodig wees.

Verminderde urinêre kalsiumuitskeiding wat deur tiasiede veroorsaak word, mag met tussenposes 'n effens verhoogde serumkalsiumkonsentrasie veroorsaak. Indien uitgesproke hiperkalsemie sou voorkom, mag dit 'n aanduiding van onderliggende hiperparatiroïedisme wees. Voordat toetse van paratiroïedfunksie uitgevoer word (sien Interaksies), moet **LISORETIC**-terapie gestaak word.

Verhoogde cholesterol- en trigliseriedvlakke mag deur tiasied-diuretikumterapie veroorsaak word.

Tiasied-diuretika mag hiperurisemie en/of jig in sekere pasiënte presipiteer. As gevolg van die verhoging in urinêre uriensuur wat deur lisinopriël veroorsaak word, mag hiperurisemie verminder word deur **LISORETIC** wat albei komponente bevat.

Sensitiwiteit/Angio-edeem

Angio-edeem van die gesig, ekstremitate, lippe, tong, glottis en/of larinks is met angiotensienomsettingsensiem-inhibeerders, insluitend lisinopriël, in pasiënte aangemeld. In sulke gevalle behoort **LISORETIC** onmiddellik gestaak, en toepaslike maatreëls ingestel te word om volkome resoluëie van simptome te verseker voordat die pasiënt ontslaan word. In gevalle waar die swelling slegs tot die gesig en lippe beperk is, verdwyn die toestand gewoonlik sonder behandeling, alhoewel antihistamiene nuttig gevind is om simptome te verlig.

Angio-edeem wat met edeem van die larinks voorkom, kan noodlottig wees. Waar die tong, glottis of larinks betrek word en moontlik lugwegobstruksie mag veroorsaak, moet toepaslike noodterapie vinnig toegepas word. Dit mag toediening van adrenalien en/of onderhoud van 'n patente lugweg insluit. Die pasiënt moet onder noukeurige mediese toesig verkeer totdat volkome en volgehoue resoluëie van simptome plaasgevind het. Hierdie pasiënte moet nooit weer enige AOE-inhibeerder ontvang nie.

Pasiënte met 'n geskiedenis van angio-edeem wat onverwant is aan AOE-inhibeerderterapie, mag aan 'n verhoogde risiko van angio-edeem blootgestel wees

wanneer hulle 'n AOE-inhibeerder ontvang (sien ook Kontra-indikasies).

In pasiënte wat tiasiede ontvang, mag sensitiwiteitsreaksies met of sonder 'n geskiedenis van allergie of brongiale asma, voorkom.

In pasiënte wat tiasiede ontvang, mag sensitiwiteitsreaksies met, of sonder 'n geskiedenis van allergie of brongiale asma, voorkom. Verergering of aktivering van sistemiese lupus eritematose is met die gebruik van tiasiede aangemeld.

Ras

LISORETIC veroorsaak 'n hoër voorkoms van angio-edeem in swart pasiënte as in pasiënte wat nie swart is nie.

Desensitisering

Pasiënte wat AOE-inhibeerders tydens behandeling vir desensitisering ontvang (bv. hymenoptera gif), het anafilaktoïed reaksies ontwikkel. Toe AOE-inhibeerders tydelik weerhou is, kon hierdie reaksies vermy word maar hulle het weer voorgekom toe blootstelling per abuis gebeur het.

Hoes

'n Nie-produktiewe, aanhoudende hoes is met die gebruik van AOE-inhibeerders aangemeld. Die hoes verdwyn na staking van terapie. AOE-inhibeerder-geïnduseerde hoes behoort as deel van die differensiële diagnose van hoes oorweeg te word.

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VAN DIE BEHANDELING DAARVAN:

Behandeling is simptomaties en ondersteunend. Geen spesifieke inligting oor die behandeling van oordosering met **LISORETIC** is beskikbaar nie. Therapie met **LISORETIC** moet gestaak word en die pasiënt moet onder uiters noukeurige toesig gehou word. Voorgestelde maatreëls sluit in induksie van emese en/of maagspoeling indien inname onlangs voorgekom het, en korreksie van dehidrasie, elektrolietwanbalans en hipotensie met behulp van gevestigde prosedures.

Lisinopriël: Die waarskynlikste eienskappe van oordosering mag hipotensie, elektrolietversteuring en nierversaking insluit. Behandeling is simptomaties en ondersteunend.

Hidrochloortiasied: Die mees algemene tekens en simptome wat waargeneem word, is dié wat deur elektrolietuitputting (hipokalemie, hipochloremie, hiponatremie) en dehidrasie as gevolg van oormatige diuresis, veroorsaak word. Indien digitalis gelyktydig gebruik is, mag hipokalemie hartaritmieë versterk.

IDENTIFIKASIE

LISORETIC 10/12,5: 'n Perske-kleurige, ronde, 6 mm bikonvekse tablet, gemerk 'LH'.

LISORETIC 20/12,5: 'n Wit, ronde, 8 mm bikonvekse, gekepte tablet., gemerk 'LH'.

AANBIEDING

PVC/PVDC Aluminium stulpakkings van 30 tablette.

BERGINGSINSTRUKSIES

Bewaar onder 25°C. Beskerm teen lig.

Hoe stulpakking in houer tot nodig vir gebruik.

HOU BUITE BEREIK VAN KINDERS.

REGISTRASIENOMMERS:

LISORETIC 10/12,5: 37/7.1.3/0475

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