PROFESSIONAL INFORMATION

SCHEDULING STATUS: [S3]

PROPRIETARY NAME AND DOSAGE FORM:

LISINOPRIL CO UNICORN 10/12,5 tablets.

LISINOPRIL CO UNICORN 20/12,5 tablets.

COMPOSITION:

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

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

LISINOPRIL CO UNICORN 10/12,5
contains sugar (mannitol 18,7 mg/tablet)
LISINOPRIL CO UNICORN 20/12,5
contains sugar (mannitol 38,30 mg/tablet)

Inactive ingredients:

Croscarmellose sodium, dibasic calcium phosphate dihydrate, magnesium stearate, Pigment blend PB-27222 Beige (10 mg tablet only), pregelatinised maize starch.

PHARMACOLOGICAL CLASSIFICATION:

A 7.1.3 Vascular medicine - Other hypotensives.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

LISINOPRIL CO UNICORN 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.

Lisinopril:

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:

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 the thiazides are unknown. Thiazides do not usually affect normal blood pressure.

Non-melanoma skin cancer:

Based on available data from epidemiological studies, a cumulative dose-dependent association between hydrochlorothiazide and non-melanoma skin cancer (NMSC) has been observed. One study included a population comprised of 71 533 cases of basal cell carcinoma (BCC) and of 8 629 cases of squamous cell carcinoma (SCC) matched to 1 430 833 and 172 462 population controls respectively. High hydrochlorothiazide use (≥ 50 000 mg cumulative) was associated with an adjusted odds ratio (OR) of 1,29 (95 %CI: 1,23 – 1,35) for BCC and 3,98 (95 % CI: 3,68 – 4,31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. A 50 000 mg cumulative dose corresponds to 12,5 mg hydrochlorothiazide taken daily for about 11 years. Another study showed a possible association between lip cancer (SCC) and exposure to hydrochlorothiazide: 633 cases of lip-cancer were matched with 63 067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2,1 (95 % CI: 1,7 – 2,6) increasing to OR 3,9 (3,0 – 4,9) for high use (~ 25 000 mg) and OR 7,7 (5,7 – 10,5)

for the highest cumulative dose (~ 100 000 mg) (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Incidence rates of NMSC depend on skin phenotypes and other factors leading to different baseline risks and varying incidence rates in different countries. Estimated incidence rates vary across different regions in Europe and are estimated at rates of around 1 to 34 cases per 100 000 inhabitants per year for SCC and 30 to 150 per 100 000 inhabitants per year for BCC. Based on the results of the two Danish epidemiological studies, this risk may increase approximately 4 to 7,7-fold for SCC and 1,3-fold for BCC depending on the cumulative dose of hydrochlorothiazide.

Pharmacokinetic properties:

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

The combination tablet is bioequivalent to concomitant administration of the separate entities.

Lisinopril

Absorption:

Lisinopril is absorbed slowly, variably and incompletely after oral administration. Based on urinary recovery, the mean extent of absorption of lisinopril is approximately 30 %, with interpatient variability (6 - 60 %) at all doses tested (5 - 80 mg).

Following oral administration of lisinopril, peak serum concentrations

occur within about 7 hours.

The absolute bioavailability is reduced approximately 16 % in patients with heart failure.

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 enzyme (ACE).

Elimination:

Lisinopril does not undergo metabolism and absorbed medicine is excreted unchanged entirely in the urine.

On multiple dosing lisinopril has an effective half-life of accumulation of 12 hours. The clearance of lisinopril in healthy subjects is approximately 50 ml/min. Declining serum concentrations exhibit a prolonged terminal phase, which does not contribute to lisinopril accumulation. This terminal phase probably represents saturable binding to ACE and is not proportional to dose.

Hepatic impairment:

Impairment of hepatic function in cirrhotic patients resulted in a decrease in lisinopril absorption (about 30 % as determined by urinary recovery) but an increase in exposure (approximately 50 %) compared to healthy subjects due to decreased clearance.

Renal impairment:

Impaired renal function decreases elimination of lisinopril, which is excreted via the kidneys, but this decrease becomes clinically important only 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	**n**	**C_{max}**	**T_{max}**	**AUC**	**$t_{1/2}$**
Measured by		**(ng/ml)**	**(hr)**	**(0-24 hrs) (ng/hr/ml)**	**(hr)**
creatinine clearance					
>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

With a creatinine clearance of 30 - 80 ml/min, mean AUC was increased by 13 % only, while a 4 to 5-fold increase in mean AUC was observed with creatinine clearance of 5 - 30 ml/min.

Lisinopril can be removed by dialysis. During 4 hours of haemodialysis, plasma lisinopril concentrations decreased on average by 60 %, with a dialysis clearance between 40 and 55 ml/min.

Heart Failure

Patients with heart failure have a greater exposure of lisinopril when compared to healthy subjects (an increase in AUC on average of 125 %), but based on the urinary recovery of lisinopril, there is reduced absorption of approximately 16 % compared to healthy subjects.

Elderly

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

Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

INDICATIONS:

LISINOPRIL CO UNICORN 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.

CONTRAINDICATIONS:

- Known hypersensitivity to lisinopril, hydrochlorothiazide or any of the excipients of **LISINOPRIL CO UNICORN**.
- Patients with a history of previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and lip.
- Patients with a history of angioedema relating to previous treatment with an ACE inhibitor. These patients must never

be given these medicines again.

- Concomitant use of fluoroquinolones with angiotensin-converting enzyme (ACE) inhibitors or renin-angiotensin receptor blockers is contraindicated in patients with moderate to severe renal impairment (see **WARNINGS AND SPECIAL PRECAUTIONS**).
- Patients with hereditary or idiopathic angioedema (see **WARNINGS AND SPECIAL PRECAUTIONS**).
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Anuria, severe renal function impairment (creatinine clearance less than 30 ml/min).
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic stenosis.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride.
- Porphyria.
- Thiazide diuretics in (fixed dose) combination with **LISINOPRIL CO UNICORN** should not be given to patients with Addison's disease.
- Lithium therapy: Concomitant administration with **LISINOPRIL CO UNICORN** may lead to toxic blood concentrations of lithium.
- Hypersensitivity to other sulphonamide-derived medicines.
- Severe hepatic impairment, cholestasis and biliary obstructive disorders.
- Concomitant administration with aliskiren-containing medicines

in patients with diabetes mellitus (type I or II) or with moderate to severe renal impairment (GFR < 60 ml/min/1.73 m2) (see **WARNINGS AND SPECIAL PRECAUTIONS and INTERACTIONS).**

- Symptomatic hyperuricaemia/gout.
- Pregnancy and lactation (see **HUMAN REPRODUCTION**).
- Safety and efficacy have not been established in children.

WARNINGS AND SPECIAL PRECAUTIONS:

Pregnancy

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

Acute kidney injury

Concomitant use of fluoroquinolones and angiotensin-converting enzyme (ACE) inhibitors or renin-angiotensin receptor blockers 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 treatment with ACE inhibitors or renin-angiotensin receptor blockers.

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. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC. Patients taking **LISINOPRIL CO UNICORN** 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 preventive measures such as limited exposure to sunlight and UV rays and, in the case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. **LISINOPRIL CO UNICORN** should not be used by patients who have had previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and/or lip (see **CONTRAINDICATIONS**).

Renal transplantation:

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

Anaphylactoid reactions in haemodialytic patients:

The use of **LISINOPRIL CO UNICORN** is not indicated in patients requiring dialysis for renal failure.

Anaphylactoid reactions have been reported in patients, undergoing certain haemodialysis procedures with certain dialysis membranes (e.g. with the high-flux membranes AN 69 and during low-density lipoproteins (LDL) 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.

Anaphylactoid reactions related to low-density lipoproteins (LDL) Apheresis:

In rare occasions, patients treated with ACE inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate has shown life threatening anaphylactic reactions. These symptoms could be avoided by temporary discontinuation of the treatment with ACE inhibitors before each apheresis.

Hypotension and Electrolyte/Fluid Imbalance:

Symptomatic hypotension is rarely 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 **INTERACTIONS, SIDE EFFECTS,** and **WARNINGS AND SPECIAL PRECAUTIONS**).

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 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 % 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 components may be used appropriately as monotherapy.

In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with **LISINOPRIL CO UNICORN**. This effect is anticipated and is not usually a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of **LISINOPRIL CO UNICORN** may be necessary.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy:

As with other ACE inhibitors, **LISINOPRIL CO UNICORN** should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

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

There is evidence that the concomitant use of ACE inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure).Dual blockade of RAAS through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended see **INTERACTIONS**).

ACE inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

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.)

LISINOPRIL CO UNICORN 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 **LISINOPRIL CO UNICORN.**

In patients with heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function Acute renal failure, usually reversible, has been reported in this situation.

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. 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.

Prior diuretic therapy

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

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.

Patients receiving **LISINOPRIL CO UNICORN** who develop jaundice or marked elevations of hepatic enzymes should discontinue **LISINOPRIL CO UNICORN** and receive appropriate medical follow-up.

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 is considered to be due to this mechanism, it can be corrected by volume expansion.

Metabolic and Endocrine Effects:

ACE inhibitor and thiazide 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 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 **LISINOPRIL CO UNICORN** which contains both components.

Electrolyte imbalance:

As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia, and hypochloremic 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 hyponatremia 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 thiazides may result in intermittent and a slightly raised serum calcium concentration. Should marked hypercalcaemia occur, it may be evidence of underlying hyperparathyroidism. **LISINOPRIL CO UNICORN** therapy should be discontinued before carrying out tests for parathyroid function (see

INTERACTIONS).

Hyperkalaemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including lisinopril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, diabetes mellitus, or those using concomitant potassium-sparing diuretics, 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, regular monitoring of serum potassium is recommended (see section **INTERACTIONS**).

Hypersensitivity/Angioedema:

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients with ACE inhibitors, including lisinopril.

In such cases **LISINOPRIL CO UNICORN** 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. 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 adrenaline and/or maintenance of a patient airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms have 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 **CONTRAINDICATIONS**).
Patients taking concomitant mammalian target of rapamycin (mTOR) inhibitors (e.g. sirolimus, everolimus, temsirolimus) therapy may be at increased risk of angioedema.
In patients receiving thiazides, sensitivity reactions may occur with or without a history of allergy or bronchial asthma.

Systemic lupus erythematosus:

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

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.

Neutropenia/agranulocytosis:

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported for patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors neutropenia occurs rarely. Neutropenia and agranulocytosis are reversible after discontinuation of the ACE inhibitor. Lisinopril 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. The cough resolves 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 generally not recommended (see **INTERACTIONS**).

Anti-doping test:

The hydrochlorothiazide contained in this medication could produce a positive analytic result in an anti-doping test.

Photosensitivity:

Cases of photosensitivity reactions have been reported with thiazide diuretics (see **SIDE EFFECTS**). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If re-administration of **LISINOPRIL CO UNICORN** is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Porphyria:

Hydrochlorothiazide has been classified as probably not porphyrinogenic, it may be used as a compound of first choice and no precautions are needed.

Acute Angle-Closure Glaucoma:

Hydrochlorothiazide, a sulphonamide, as contained in **LISINOPRIL CO UNICORN** 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 **LISINOPRIL CO UNICORN** initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss.

The primary treatment is to discontinue hydrochlorothiazide and therefore **LISINOPRIL CO UNICORN** 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 **SIDE EFFECTS**).

Ethnic Groups:

LISINOPRIL CO UNICORN causes a higher rate of angioedema in black patients than in non-black patients.

As with other ACE inhibitors, 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.

Effects on ability to drive and use machines:

LISINOPRIL CO UNICORN may have a mild to moderate influence on a patient's ability to drive and use machines, especially at the onset of treatment or when the dose is modified, and also when used in combination with alcohol. These effects depend on the individual's susceptibility. Patients should be cautioned that they may experience dizziness or tiredness when driving vehicles or operating machinery.

INTERACTIONS:

Fluoroquinolones

Concomitant use of fluoroquinolones and angiotensin-converting enzyme (ACE) inhibitors or renin-angiotensin receptor blockers may precipitate acute kidney injury (see **CONTRAINDICATIONS** and **WARNINGS AND SPECIAL PRECAUTIONS**). The concomitant use of these molecules may lead to renal impairment due to altered renal haemodynamics in particular clinical situations or with other medications that affect renal glomerular filtration.

Antihypertensive medicines

The concomitant use of **LISINOPRIL CO UNICORN** with diuretics and other hypertensive medicines may increase the hypotensive effects.
Concomitant use of glyceryl nitrate and other nitrates or other vasodilators may further reduce the blood pressure.
Clinical trial data has shown that dual blockade of the RAAS through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS acting medicine.

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. The combination of **LISINOPRIL CO UNICORN** with lithium is therefore not recommended and careful monitoring of serum lithium levels should be performed if the combination proves necessary (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Potassium

The decrease in potassium caused by thiazide diuretics is usually potentiated by the effect of lisinopril. The use of potassium

supplements, potassium-sparing medicines 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 **LISINOPRIL CO UNICORN** concomitantly with any of these medicines, caution should be exercised and serum potassium should be monitored on a regular basis (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Torsades de pointes- inducing medicines

Due to the risk of hypokalaemia the concomitant administration of hydrochlorothiazide and medicines that induce torsades de pointes, e.g. some antiarrhythmics, some anti- psychotics should be used with caution.

Tricyclic antidepressants/ antipsychotics /anaesthetics

Concomitant use of certain anaesthetic medicines, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further lowering of blood pressure.

Nonsteroidal anti-inflammatory drugs (NSAIDs)

Chronic administration of NSAID (selective cyclooxygenase-2 inhibitors, acetylsalicylic acid >3 g/day and non-selective NSAIDs) may reduce the antihypertensive and diuretic effect of ACE inhibitors and thiazide diuretics. NSAID 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 are

usually reversible. Rarely, acute renal failure may occur, especially in patients with compromised renal function such as the elderly or dehydrated.

Gold

Nitritoid reactions (symptoms of vasodilatation including flushing, nausea, dizziness and hypotension, which can be very severe) following injectable gold (for example, sodium aurothiomalate) have been reported more frequently in patients receiving ACE inhibitor therapy.

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effect of ACE inhibitors.

Antidiabetics

Epidemiological studies indicate that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic medicines) may cause an increased blood glucose lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combination treatment and in patients with renal impairment.

Other antidiabetic medicines including insulin requirements in diabetic patients may be increased, decreased, or unchanged.

The hyperglycaemic effect of diazoxide may be enhanced by the hydrochlorothiazide in **LISINOPRIL CO UNICORN.**

Amphotericin B (parenteral), carbenoxolone, corticosteroids, corticotropin (ACTH) or stimulant laxatives

The potassium depleting effect of hydrochlorothiazide could be expected to be potentiated by medicines associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, amphotericin, carbenoxolone, salicylic acid derivatives). Hypokalemia may develop during concomitant use of steroids or adrenocorticotropic hormone (ACTH).

Calcium salts

The hydrochlorothiazide in **LISINOPRIL CO UNICORN** may increase serum calcium levels due to decreased excretion. If calcium supplements or vitamin D must be prescribed, serum calcium levels should be monitored, and the dose adjusted accordingly.

Pressor amines

Thiazide diuretics may decrease response to pressor amines (e.g. adrenalin). This decrease in response is not sufficient to prelude the use of pressor amines.

Non-depolarizing muscle relaxants (e.g. tubocurarine chloride)

The effect of these medicines may be potentiated by hydrochlorothiazide.

Trimethoprim/sulfamethoxazole

Concomitant administration of ACE inhibitors and thiazides with trimethoprim alone or in combination with sulfamethoxazole, increases the risk of hyperkalaemia.

Sotalol

Thiazide induced hypokalaemia can increase the risk of sotalol induced arrhythmia when these medicines are given together.

Allopurinol

Concomitant administration of ACE inhibitors and allopurinol increases the risk of renal damage and can lead to an increased risk of leucopoenia.

Ciclosporin

Concomitant treatment may increase the risk of hyperuricaemia and gout-type complications.

Lovastatin

Concomitant administration of ACE inhibitors and lovastatin increases the risk of hyperkalaemia.

Cytostatics, immunosuppressives, procainamide

The thiazide in **LISINOPRIL CO UNICORN** may reduce the renal excretion of cytotoxic medicines (e.g. cyclophosphamide, methotrexate) and potentiate their

myelosuppressive effects (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Alcohol, barbiturates or narcotics

Potentiation of orthostatic hypotension may occur.

Cardiac glycosides

Hypokalaemia may sensitise or exaggerate the response of the heart to the toxic effects of digitalis (e.g. increased ventricular irritability).

Medicines that may increase the risk of angioedema

Concomitant use of **LISINOPRIL CO UNICORN** with mammalian target of rapamycin (mTOR) inhibitors or neural endopeptidase (NEP) inhibitors (e.g. racecadotril) or tissue plasminogen activator may increase the risk of angioedema (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Colestipol and cholestyramine

These reduce the absorption of the hydrochlorothiazide in **LISINOPRIL CO UNICORN**. Therefore, **LISINOPRIL CO UNICORN** should be taken at least 1 hour before or 4 – 6 hours after the intake of these medicines.

Amantadine

The thiazide in **LISINOPRIL CO UNICORN** may increase the risk of adverse effects caused by amantadine.

HUMAN REPRODUCTION

Pregnancy

Safety in pregnancy and lactation has not been established (see **CONTRAINDICATIONS** and **WARNINGS AND SPECIAL PRECAUTIONS).**

LISINOPRIL CO UNICORN passes through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms. Oligohydramnios as well as hypotension, oliguria and anuria in new-borns, have been reported after administration of **LISINOPRIL CO UNICORN** 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 **LISINOPRIL CO UNICORN** 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 **CONTRAINDICATIONS** and **WARNINGS AND SPECIAL PRECAUTIONS).**

Hydrochlorothiazide crosses the placenta and appears in cord blood. Although studies in humans have not been done, thiazide diuretics can cause foetal harm when given to pregnant women. There have been reports of neonatal jaundice, thrombocytopenia and electrolyte imbalances after maternal use.

Lactation:

It is not known whether lisinopril is distributed into human breast milk**;** however thiazides do appear in human milk.

Owing to the potential for adverse effects on the nursing infant, breast feeding should be discontinued if the use of **LISINOPRIL CO UNICORN** is considered essential.

DOSAGE AND DIRECTIONS FOR USE:

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 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 **LISINOPRIL CO UNICORN**; 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 **LISINOPRIL CO UNICORN**, or if this is not possible, lisinopril should be given alone at a low initial dose of 5 mg. (see **WARNINGS AND SPECIAL PRECAUTIONS**).

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.)

LISINOPRIL CO UNICORN should not be used as initial therapy in any patient with renal insufficiency.

In patients with creatinine clearance of >30 and <80 ml/min, **LISINOPRIL CO UNICORN** may be used, but only after titration of the individual components (see **WARNINGS AND SPECIAL PRECAUTIONS**).

The recommended dose of lisinopril, when used alone, in mild renal insufficiency, is 5 to 10 mg.

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

LISINOPRIL CO UNICORN:

The most commonly reported adverse effects with the lisinopril/hydrochlorothiazide combination are cough, dizziness, hypotension and headache.

Adverse events reported with the individual components, lisinopril and hydrochlorothiazide may be potential adverse effects with **LISINOPRIL CO UNICORN**. Adverse effects of the individual components are detailed

below.

Lisinopril:

Adverse events reported with the use of lisinopril alone include:

System Organ Class	Frequency	Undesirable effects
Blood and lymphatic	*Less frequent:*	Decreases in haemoglobin,
system disorders		decreases in haematocrit,
		anaemia, haemolytic anaemia,
		neutropenia, agranulocytosis
		thrombocytopenia, leucopenia
		hyperkalaemia, hyponatremia
		lymphadenopathy,
		autoimmune disease, bone
		marrow depression.
Immune system	*Less frequent:*	skin rash, photosensitivity,
disorders		alopecia, Stevens-Johnson
		Syndrome.
	Frequency	Anaphylactic/anaphylactoid
	unknown:	reaction
Endocrine disorders	*Less frequent:*	Syndrome of inappropriate
		antidiuretic hormone secretion.
Metabolism and	*Less frequent:*	Taste disturbances,
nutrition disorders		hyponatraemia, pancreatitis,
		hypoglycaemia.

Psychiatric	*Less frequent:*	Mood alterations, mental
disorders		confusion and sleep
		disturbances, depressive
		symptoms
	Frequency	Hallucinations.
	unknown:	
Nervous system	*Frequent:*	Dizziness, headache, fatigue,
disorders		syncope,
	Less frequent:	Vertigo, taste
		disturbance, hypoaesthesia,
		paraesthesia, olfactory
		disturbance.
Cardiac disorders:	*Less frequent:*	Myocardial infarction or
		cerebrovascular accident,
		tachycardia,
		palpitations, chest pain.
Vascular disorders:	*Frequent:*	Orthostatic effects (including
		orthostatic hypotension),
	Less frequent:	Raynaud’s syndrome.
	Frequency	Flushing.
	unknown:	

Respiratory,	*Frequent:*	Cough,
thoracic and	*Less frequent:*	bronchospasm, rhinitis,
mediastinal		sinusitis, pulmonary
disorders		infiltrates, allergic
		alveolitis/eosinophilic
		pneumonia.
Gastrointestinal	*Frequent:*	Diarrhoea, vomiting.
disorders	*Less Frequent:*	Nausea, gastrointestinal
		disturbances, stomatitis,
		abdominal pain,
		dry mouth,
		intestinal angioedema,
		pancreatitis, indigestion.
Hepatobiliary	*Less frequent:*	Hepatitis
disorders		(hepatocellular or
		cholestatic), jaundice,
		hepatic failure,
		elevated liver enzymes and
		bilirubin.
Skin and	*Less frequent:*	Rash, pruritus.
subcutaneous tissue		hypersensitivity/angioneurotic
disorders		oedema: angioneurotic
		oedema of the face,

		extremities, lips, tongue,
		glottis, and/or
		larynx, urticaria, alopecia,
		psoriasis,
		diaphoresis, pemphigus, toxic
		epidermal necrolysis,
		Stevens Johnson
		syndrome, erythema
		multiforme,
		cutaneous pseudolymphoma*
Musculoskeletal,	*Less frequent:*	Muscle cramps.
bone and connective		
tissue disorders:		
Renal and urinary	*Frequent:*	Renal dysfunction.
disorders	*Less frequent:*	Diaphoresis, uraemia,
		oliguria/anuria, renal
		dysfunction, acute renal
		failure, proteinuria.
Reproductive	*Less frequent:*	Impotence,
system and breast		gynaecomastia.
disorders		
General disorders	*Less frequent:*	Asthenia, fatigue.
and administration		
site conditions		

Investigations	*Less frequent:*	Increases in blood urea,
		increases in serum creatinine,
		hyperkalaemia,
		hyponatraemia.
*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:		
System Organ Class	**Frequency**	**Undesirable effects**
Infections and	*Frequency*	Sialadenitis.
infestations	*unknown:*	
Neoplasms benign	*Frequency*	Non-melanoma skin cancer
and malignant	*unknown:*	(basal cell carcinoma and
(including cysts		squamous cell carcinoma)
and polyps):		
Blood and lymphatic	*Less frequent:*	hyponatremia,
system disorders		hypokalaemia,
		hypochloraemic alkalosis,
		granulocytopenia,

	Frequency	Leukopenia, neutropenia,
	unknown:	agranulocytosis,
		thrombocytopenia, aplastic
		anaemia, haemolytic
		anaemia, bone marrow
		depression.
Immune system	*Less frequent:*	Hypersensitivity reaction
disorders		(rash, fever, pulmonary
		oedema, pneumonitis,
		anaphylaxis, toxic epidermal
		necrolysis).
Metabolism and	*Less frequent:*	Electrolyte imbalance
nutrition disorders		cholecystitis,
		gallstones,
	Frequency	Anorexia, hyperglycaemia,
	unknown:	glycosuria, hyperuricaemia,
		electrolyte imbalance
		(including hyponatraemia,
		hypokalaemia, hypochloremic
		alkalosis and
		hypomagnesaemia), increases
		in cholesterol and
		triglycerides, gout.

Psychiatric	*Frequency*	Restlessness, depression,
disorders	*unknown:*	sleep disturbance
Nervous system	*Frequent:*	Vertigo,
disorders		hypoesthesia,
		dizziness,
		headache, sleep
		disturbances.
	Frequency	Loss of appetite,
	unknown:	paraesthesia,
		lightheadedness.
Eye disorders:	*Frequency*	Xanthopsia, transient blurred
	unknown:	vision, acute myopia, acute
		angle-closure glaucoma.
Ear and labyrinth	*Frequency*	Vertigo.
disorders:	*unknown:*	
Cardiac disorders:	*Less frequent:*	Cardiac arrhythmias.
	Frequency	Postural hypotension
	unknown:	
Vascular disorders:	*Less frequent:*	Orthostatic hypotension,
	Frequency	Necrotising angiitis (vasculitis,
	unknown:	cutaneous vasculitis).
Respiratory,	*Frequency*	Respiratory distress

thoracic and	*unknown*	(including pneumonitis,
mediastinal		pulmonary oedema)
disorders		
Gastrointestinal	*Less frequent:*	gastrointestinal disturbances,
disorders		nausea, vomiting,
		intestinal
		ulceration, pancreatitis
	Frequency	Gastric irritation, diarrhoea,
	unknown:	constipation, pancreatitis.
Hepatobiliary	*Frequency*	Jaundice (intrahepatic
disorders	*unknown:*	cholestatic jaundice).
Skin and	*Frequent:*	Skin rash, purpura,
subcutaneous tissue		photosensitivity,
disorders		
	Frequency	Photosensitivity reactions,
	unknown:	rash, systemic lupus
		erythematosus, cutaneous
		lupus erythematosus-like
		reactions, reactivation of
		cutaneous lupus
		erythematosus, urticaria,
		anaphylactic reactions, toxic
		epidermal necrolysis.
Musculoskeletal and	*Less frequent:*	Muscle pain and

connective tissue		cramps.
and bone disorders:		
	Frequency	Muscle spasm, muscle
	unknown:	weakness.
Renal and urinary	*Less frequent:*	Renal failure,
disorders		non-opaque urate calculi.
	Frequency	Renal dysfunction, interstitial
	unknown:	nephritits.
Reproductive	*Less frequent:*	Sexual dysfunction.
system and breast		
disorders		
General disorders	*Frequency*	Fever, weakness.
and administration	*unknown:*	
site conditions		

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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 recommended treatment of overdose is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the supine position. If available, treatment with angiotensin II infusion

and/or intravenous catecholamines may also be considered. If ingestion is recent, take measures aimed at eliminating lisinopril (e.g. emesis, gastric lavage, administration of absorbents and sodium sulphate). Lisinopril may be removed from the general circulation by haemodialysis. Pacemaker therapy is indicated for therapy resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored frequently. Bradycardia or extensive vagal reactions should be treated by administering atropine.

IDENTIFICATION:

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

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

PRESENTATION:

LISINOPRIL CO UNICORN 10/12,5 : PVC/PVDC Aluminium blister packs of 30 tablets, contained in a printed outer carton.

LISINOPRIL CO UNICORN 20/12,5 : PVC/PVDC Aluminium blister packs of 30 tablets, contained in a printed outer carton.

STORAGE INSTRUCTIONS:

Store at or below 25ºC. Protect from light.

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

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

LISINOPRIL CO UNICORN 10/12,5 : 37/7.1.3/0477

LISINOPRIL CO UNICORN 20/12,5 : 37/7.1.3/0478

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE

CERTIFICATE OF REGISTRATION:

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