INSTRUCTION
for medical use

STATORAM®-H

Composition:
active substance: lisinopril, hydrochlorothiazide;
1 tablet contains lisinopril dihydrate equivalent to lisinopril 20 mg and hydrochlorothiazide 12.5 mg.
excipients: mannitol (E 421), calcium hydrogen phosphate, corn starch, pregelatinized starch, colloidal anhydrous silica, magnesium stearate.

Pharmaceutical form. Tablets.
Basic physical and chemical properties: white or almost white round flat tablets debossed with "K" on one side and plain on the other side.

Pharmacotherapeutic group. Angiotensin-converting enzyme inhibitors and diuretics. ATC code C09B A03.

Pharmacological properties.
Pharmacodynamics.
Statoram®-H is a fixed dose combination product containing lisinopril, an inhibitor of angiotensin converting enzyme (ACE) and hydrochlorothiazide, a thiazide diuretic. Both components have complementary modes of action and exert an additive antihypertensive effect.
Lisinopril
Lisinopril is a peptidyl dipeptidase inhibitor. It inhibits the angiotensin converting enzyme (ACE) that catalyses the conversion of angiotensin I to the vasoconstrictor peptide, angiotensin II. Angiotensin II 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. The latter decrease may result in an increase in serum potassium concentration.
While the mechanism through which lisinopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, lisinopril is antihypertensive even in patients with low-renin hypertension. ACE is identical to kininase II, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodilatory peptide, play a role in the therapeutic effects of lisinopril remains to be elucidated.
Hydrochlorothiazide
Hydrochlorothiazide is a diuretic and an antihypertensive agent. It affects the distal renal tubular mechanism of electrolyte reabsorption 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 effect of the thiazides is unknown. Thiazides do not usually affect normal blood pressure.
Pharmacokinetic properties.
There is no clinically relevant pharmacokinetic interaction between lisinopril and hydrochlorothiazide. The combination tablet is bioequivalent to concomitant administration of the separate entities.
Lisinopril
Absorption
Following oral administration of lisinopril, peak serum concentrations occur within about 7 hours, although there was a trend to a small delay in time taken to reach peak serum concentrations in acute myocardial infarction patients. Based on urinary recovery, the mean extent of absorption of

lisinopril is approximately 25%, with interpatient variability (6-60%) at all doses tested (5-80 mg). The absolute bioavailability is reduced approximately 16% in patients with heart failure.
Lisinopril absorption is not affected by the presence of food.

Distribution

Lisinopril does not appear to bind to other serum proteins other than to circulating angiotensin-converting enzyme (ACE).
Preclinical studies have shown that lisinopril crosses the blood-brain barrier poorly.

Elimination

Lisinopril does not undergo metabolism and absorbed drug is excreted unchanged entirely in the urine. On multiple dosing lisinopril has an effective half-life of accumulation of 12.6 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 drug 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.
With a creatinine clearance of 30–80ml/min, mean AUC was increased by 13% only, while a 4–5 fold increase in mean AUC was observed with creatinine clearance of 5–30ml/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

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

Hydrochlorothiazide

Absorption

When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours.

Distribution

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

Elimination

At least 61% of the dose is eliminated unchanged within 24 hours. After oral hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts 6 to 12 hours.

Clinical characteristics.

Indications.

Statoram®-H is indicated in the management of mild to moderate hypertension in patients who have been stabilised on the individual components given in the same proportions.

Contraindications.

Hypersensitivity to the active substances or any excipients of the drug.
Hypersensitivity to any other ACE inhibitor.
Hypersensitivity to any sulfonamide drugs.

History of angioneurotic edema associated with prior ACE inhibitor therapy.
Hereditary or idiopathic angioneurotic edema.
Pregnancy and pregnancy planning.
Severe renal impairment (creatinine clearance <30 ml/min).
Anuria.
Severe hepatic impairment.
Concomitant use of Statoram®-H with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (glomerular filtration rate <60 ml/min/1.73 m2).

Interaction with other medicinal products and other forms of interaction.
Antihypertensive agents
When combined with other antihypertensive agents, additive falls in blood pressure may occur. Concomitant use of glyceryl trinitrate and other nitrates or other vasodilators may further reduce the blood pressure.
The combination of lisinopril with aliskiren-containing medicines should be avoided (see sections "Contraindications" and "Special warnings and precautions for use").
Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone system (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 agent (see sections "Contraindications", "Special warnings and precautions for use" and "Pharmacodynamic properties").
Medicines increasing the risk of angioedema
Concomitant use of ACE inhibitors with m-TOR inhibitors (e.g. temsirolimus, sirolimus, everolimus) or with neutral endopeptidase inhibitors (e.g. racecadotril) or tissue plasminogen activators may increase the risk of angioedema.
Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Diuretic agents and ACE inhibitors reduce the renal clearance of lithium and pose a high risk of lithium toxicity. The combination of lisinopril and hydrochlorothiazide with lithium is therefore not recommended and careful monitoring of serum lithium levels should be performed if the combination proves necessary (see section "Special warnings and precautions for use").
Potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutes and other medicinal products that may increase serum potassium levels
The potassium losing effect of thiazide diuretics is usually attenuated by the potassium conserving effect of lisinopril. The use of potassium supplements, potassium-sparing preparations or salts containing potassium, and other drugs that may increase serum potassium, especially in patients with renal impairment or diabetes, may lead to a significant increase in serum potassium. If concomitant use of lisinopril/hydrochlorothiazide and any of these drugs is necessary, they should be used with caution and with frequent monitoring of serum potassium necessary (see section "Special warnings and precautions for use").
Torsades de pointes-inducing medicinal products
Because of the risk of hypokalaemia the concomitant administration of hydrochlorothiazide and medicinal products that induce torsades de pointes, e.g. some antiarrhythmics, some anti-psychotics and other drugs known to induce torsades de pointes, should be used with caution.
Tricyclic antidepressants/ antipsychotics /anaesthetics
Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further lowering of blood pressure (see section "Special warnings and precautions for use").
Non-steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid
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 can reduce the antihypertensive effect of ACE inhibitors. Thiazides may decrease arterial responsiveness to noradrenaline, but not enough to rule out the effect of a drug that increases blood pressure.

Antidiabetics

Treatment with a thiazide diuretic may impair glucose tolerance. This phenomenon appeared to be more likely to occur during the first 2 weeks of combination treatment and in patients with renal impairment. Dose adjustment of insulin or oral hypoglycaemic agents may be required in patients with diabetes mellitus. The hyperglycaemic effect of diazoxide may be enhanced by thiazides.

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

The potassium depleting effect of hydrochlorothiazide could be expected to be potentiated by drugs 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

Thiazide diuretics 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.

Cardiac glycosides

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

Colestyramine and colestipol

The absorption of hydrochlorothiazide is reduced by colestipol or cholestyramine. Therefore sulphonamide diuretics should be taken at least 1 hour before or 4-6 hours after intake of these agents.

Non-depolarising muscle relaxants

Thiazides may increase the responsiveness to non-depolarising skeletal muscle relaxants (e.g. tubocurarine).

Trimethoprim

Concomitant administration of ACE inhibitors and thiazides with trimethoprim increases the risk of hyperkalaemia.

Sotalol

Thiazide induced hypokalaemia can increase the risk of sotalol induced arrhythmia.

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 administration of ACE inhibitors and ciclosporin increases the risk of renal damage and hyperkalaemia. Concomitant treatment with ciclosporin 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
Thiazides may reduce the renal excretion of cytotoxic medicinal products (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects (see section "Special warnings and precautions for use").
Co-trimoxazole (trimethoprim/sulfamethoxazole)
Patients taking concomitantly co-trimoxazole (trimethoprim/sulfamethoxazole) may be at increased risk of hyperkalaemia (see section "Special warnings and precautions for use").
Thiazides may increase the risk of adverse effects caused by amantadine.
Postural hypotension may be exacerbated by concomitant use of alcohol, barbiturates or anesthetics.

Special warnings and precautions for use.
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 based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.
Patients taking HCTZ 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 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. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC (see section "Adverse reactions").
Symptomatic hypotension
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 sections "Interaction with other medicinal products and other forms of interaction" and "Adverse reactions"). Regular determination of serum electrolytes should be performed at appropriate intervals in such patients. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be monitored under close medical supervision. Particular consideration applies to patients with ischaemic heart or cerebrovascular disease, because an excessive fall 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 normal saline. A transient hypotensive response is not a contraindication for further doses. Following restoration of effective blood volume and pressure, reinstitution of therapy at reduced dosage may be possible; or either of the components may be used appropriately alone.
In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with lisinopril. 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-hydrochlorothiazide may be necessary.
Aortic and mitral valve stenosis/hypertrophic cardiomyopathy
As with other ACE inhibitors, lisinopril 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).
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 section “Special warnings and precautions for use” and “Pharmacodynamics”).
If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.
ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.
Renal function impairment
Thiazides may not be appropriate diuretics for use in patients with renal impairment. Thiazides are ineffective at creatinine clearance values of 30 ml/min or below (corresponds to moderate or severe renal insufficiency).
Lisinopril/hydrochlorothiazide should not be administered to patients with renal insufficiency (creatinine clearance less than or equal to 80 ml/min) until titration of the individual components has shown the need for the doses present in the combination tablet.
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 been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, renal function should be monitored during the first few weeks of lisinopril/hydrochlorothiazide therapy.
Some hypertensive patients with no apparent pre-existing renal disease have developed usually minor and transient 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/hydrochlorothiazide. If this is not possible, treatment should be started with lisinopril alone, in a 5 mg dose.
Renal transplantation
As there is no experience with lisinopril/hydrochlorothiazide in patients who have recently undergone kidney transplantation, the use of Statoram®-H in such patients is not recommended.
Anaphylactoid reactions in haemodialytic patients
The use of lisinopril/hydrochlorothiazide is not indicated in patients requiring dialysis for renal failure. Anaphylactoid reactions have been reported in patients, undergoing certain haemodialysis procedures (e.g. with the high-flux membranes AN 69 and during low-density lipoproteins (LDL) apheresis with dextran sulphate) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.
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 have shown life threatening anaphylactic reactions. These symptoms could be avoided by temporary discontinuation of the treatment with ACE inhibitors before each apheresis.
Hepatic impairment
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice or hepatitis and progresses to fulminant necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving lisinopril/hydrochlorothiazide who develop jaundice or marked elevations of hepatic enzymes should discontinue lisinopril/hydrochlorothiazide and receive appropriate medical follow-up.

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. If hypotension occurs 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 agents, including insulin, may be required. In diabetic patients treated with oral antidiabetic agents or insulin, glycaemia levels should be closely monitored during the first month of treatment with an ACE inhibitor. Latent diabetes mellitus may become manifest during thiazide therapy.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Thiazide therapy may precipitate hyperuricaemia and/or gout in certain patients. However, lisinopril may increase urinary uric acid and thus may attenuate the hyperuricaemia effect of hydrochlorothiazide.

Electrolyte imbalance

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

Thiazides, including 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 (nausea or vomiting). Dilutional hyponatraemia may occur in oedematous patients in hot weather. Chloride deficit is generally mild and does not require treatment. Thiazides have been shown to increase the urinary excretions of magnesium, which may result in hypomagnesaemia.

Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Hyperkalaemia

During treatment with ACE inhibitors, including lisinopril, there was an increase in serum potassium (hyperkalemia). The risk of hyperkalaemia is higher in patients with renal insufficiency, diabetes mellitus, concomitant use of potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes, concomitant use of drugs that increase serum potassium (e.g. heparin, a combination of trimethoprim/sulfamethoxazole known as co-trimoxazole). If such concomitant treatment is required, serum potassium should be monitored regularly.

Diabetic patients

Patients with diabetes mellitus who have taken oral antidiabetic drugs or insulin should have careful glycemic control during the first month of ACE inhibitor therapy.

Hypersensitivity/angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported uncommonly in patients treated with ACE inhibitors, including lisinopril. Angioedema may occur at any time during therapy. In such cases, lisinopril should be discontinued promptly and appropriate treatment and monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx, are likely to experience airway obstruction, especially those with a history of airway surgery. In such cases emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred. ACE inhibitors cause a higher rate of angioedema in black patients than in non-black patients.
Patients with a history of angioneurotic edema not associated with an ACE inhibitor may be at increased risk of developing angioneurotic edema in response to drugs in this group.
Patients taking concomitant selective immunosuppressants (e.g. sirolimus, everolimus, temsirolimus) may be at increased risk of angioneurotic edema (e.g. airway or tongue edema, with or without damage) (see section "Interaction with other medicinal products and other forms of interaction").
In patients receiving thiazides, hypersensitivity 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.
Desensitization
Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have sustained anaphylactoid reactions. In the same patients, 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.
Race
ACE inhibitors cause 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.
Cough
Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and 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.
Anti-doping test
The hydrochlorothiazide contained in this medication could produce a positive analytic result in an anti-doping test.
Pregnancy
ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections "Contraindications" and "Use during pregnancy or lactation").

Use during pregnancy and lactation.

Pregnancy

ACE inhibitors

The use of ACE inhibitors is not recommended in the first trimester of pregnancy (see section "Special warnings and precautions for use"). The use of ACE inhibitors is contraindicated in the second and third trimesters of pregnancy (see sections "Contraindications" and "Special warnings and precautions for use").

The available data on the risk of teratogenic effects with ACE inhibitors during the first trimester of pregnancy were not conclusive; however, a small increase in this risk cannot be ruled out. While continued ACE inhibitor therapy is considered necessary, patients planning to become pregnant should be switched to alternative antihypertensive therapy, including those that have an established safety profile for use during pregnancy. If pregnancy occurs, treatment with ACE inhibitors should be stopped immediately and, if necessary, alternative therapy should be started.

The use of ACE inhibitors during the second and third trimesters of pregnancy is known to cause fetotoxic effects in humans (decreased renal function, oligohydroamnion, slowed ossification of the skull bones) and neonatal toxicity (renal failure, hypotension, hyperkalemia).

If ACE inhibitors have been used during the third trimester of pregnancy, ultrasound monitoring of renal and cranial bone function is recommended. Newborns whose mothers have taken ACE inhibitors should be closely monitored for the possible development of hypotension (see sections "Contraindications" and "Special warnings and precautions for use").

Hydrochlorothiazide

Experience with hydrochlorothiazide during pregnancy, especially in the first trimester, is limited. There are insufficient data from animal studies.

Hydrochlorothiazide crosses the placenta. The pharmacological mechanism of action of hydrochlorothiazide suggests that the use of this drug in the II and III trimesters of pregnancy may impair fetoplacental perfusion and cause foetal and neonatal reactions such as jaundice, electrolyte imbalance and thrombocytopenia.

Hydrochlorothiazide should not be used to treat edema, hypertension or preeclampsia in pregnant women, as instead of having a beneficial effect on the course of the disease, it increases the risk of decreased plasma volume and impairs uteroplacental blood supply.

Hydrochlorothiazide should not be used to treat essential hypertension in pregnant women unless alternative drugs cannot be used.

Lactation

ACE inhibitors

As there are no data on the use of lisinopril/hydrochlorothiazide during breast-feeding, lisinopril/hydrochlorothiazide is not recommended, alternatives with a known safety profile should be preferred, especially when feeding a newborn or premature infant.

Hydrochlorothiazide

Hydrochlorothiazide is excreted in small amounts in breast milk. High doses of thiazides may increase diuresis, which may lead to decreased breast milk production.

The use of lisinopril/hydrochlorothiazide during breastfeeding is contraindicated. If no alternative treatment is possible during breast-feeding, the dose of lisinopril/hydrochlorothiazide should be as low as possible.

Ability to effect the speed of reaction when driving a car or other mechanisms.

Like other antihypertensive agents, lisinopril/hydrochlorothiazide may have minor or moderate influence on the ability to drive and use machines. The risk increases at the beginning of treatment or when changing the dose, as well as if the combination drug is combined with alcohol consumption, but this effect depends on the individual sensitivity of the patient.

The possibility of dizziness and fatigue should be taken into account when driving or operating machines.

Posology and method of administration.

Primary hypertension

The usual dosage is one tablet, administered once daily. As with all other medication taken once daily, Statoram®-H should be taken at approximately the same time each day. In general, if the desired therapeutic effect cannot be achieved in a period of 2 to 4 weeks at this dose level, the dose can be increased to two tablets administered once daily.

Renal impairment

Thiazides should not be used in patients with impaired renal function, they are ineffective in moderate or severe renal insufficiency (creatinine clearance ≤ 30 ml/min).

Statoram®-H is not to be used as initial therapy in any patient with renal insufficiency.

In patients with creatinine clearance of >30 and <80 ml/min, Statoram®-H may be used, but only after titration of the individual components. The recommended dose of lisinopril, when used alone, in mild renal insufficiency, is 5 to 10 mg.

Prior diuretic therapy

Symptomatic hypotension may occur following the initial dose of Statoram®-H; this is more likely in patients who are volume and/or salt depleted (as a result of prior diuretic therapy). The diuretic therapy should be discontinued for 2–3 days prior to initiation of therapy with Statoram®-H. If this is not possible, treatment should be started with lisinopril alone, in a 5 mg dose.

Elderly

No adjustment of dosage is required.

In clinical studies the efficacy and tolerability of lisinopril and hydrochlorothiazide, administered concomitantly, were similar in both elderly and younger hypertensive patients.

Lisinopril, within a daily dosage range of 20 to 80 mg, was equally effective in the elderly (65 years or over) and non-elderly hypersensitive patients, monotherapy with lisinopril was as effective in reducing diastolic blood pressure as monotherapy with either hydrochlorothiazide or atenolol. Age did not affect the tolerability of lisinopril.

Children.

The safety and efficacy of lisinopril/hydrochlorothiazide in children have not been established.

Overdosage.

Symptoms

Limited data are available for overdose in humans. Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough.

Additional symptoms of hydrochlorothiazide overdose are increased diuresis, depression of consciousness (incl. coma), convulsions, paresis, cardiac arrhythmias and renal failure.

If digitalis has also been administered hypokalaemia may accentuate cardiac arrhythmias.

Management

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 (see section “Pharmacological properties”). 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.

Adverse reactions.

Lisinopril.

Blood and lymphatic system disorders: decreases in haemoglobin, decreases in haematocrit, bone marrow depression, anaemia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis (see section 4.4), haemolytic anaemia, lymphadenopathy, autoimmune disease.
Immune system disorders: anaphylactic/anaphylactoid reaction.
Endocrine disorders: syndrome of inappropriate antidiuretic hormone secretion (SIADH).
Metabolism and nutrition disorders: hypoglycaemia.
Nervous system disorders: dizziness, headache, syncope, paresthesia, vertigo, taste disturbance, sleep disturbances, olfactory disturbances.
Psychiatric disorders: mood alterations, depression, hallucinations, confusion.
Cardiac and vascular disorders: arterial hypotension (including orthostatic), myocardial infarction or stroke due to significant hypotension in high-risk patients, palpitations, tachycardia, Raynaud's phenomenon, flushing.
Respiratory system disorders: cough, rhinitis, bronchospasm, sinusitis, allergic alveolitis/eosinophilic pneumonia.
Gastrointestinal disorders: diarrhea, vomiting, nausea, abdominal pain, dyspepsia, dry mouth, pancreatitis, intestinal angioneurotic edema.
Hepatobiliary disorders: increased activity of liver enzymes and serum bilirubin, hepatitis (hepatocellular or cholestatic), jaundice, liver failure*.
Skin and subcutaneous tissue disorders: rash, pruritus, hypersensitivity/angioneurotic edema (face, limbs, lips, tongue, glottis and/or larynx), urticaria, alopecia, psoriasis, sweating, severe skin disorders (pemphigus, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, cutaneous pseudolymphoma **).
Renal and urinary disorders: renal dysfunction, uremia, acute renal failure, oliguria/anuria.
Reproductive system and breast disorders: impotence, gynecomastia.
General disorders: fatigue, asthenia.
Laboratory tests: increased blood urea levels, increased serum creatinine, hyperkalemia, hyponatremia.

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

**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.
Infections and infestations: sialadenitis.
Neoplasms benign, malignant and unspecified (incl cysts and polyps): Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)*.
Blood and lymphatic system disorders: leukopenia, neutropenia/agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, bone marrow depression.
Metabolism and nutrition disorders: anorexia, hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance (including hyponatraemia, hypokalaemia, hypochloremic alkalosis and hypomagnesaemia), increases in cholesterol and triglycerides, gout.
Psychiatric disorders: restlessness, depression, sleep disturbance.
Nervous system disorders: loss of appetite, paraesthesia, light-headedness..
Eye disorders: xanthopsia, transient blurred vision, acute myopia and acute angle-closure glaucoma..
Ear and labyrinth disorders: vertigo.
Cardio-vascular disorders: orthostatic hypotension, necrotizing angiitis (vasculitis, cutaneous vasculitis).
Respiratory system disorders: respiratory distress syndrome, including pneumonitis and pulmonary edema.

Gastrointestinal tract disorders: irritation of the gastric mucosa, diarrhea, constipation, pancreatitis.
Hepatobiliary disorders: jaundice (intrahepatic cholestatic jaundice).
Skin and subcutaneous tissue disorders: photosensitivity reactions, rash, systemic lupus erythematosus, cutaneous lupus-like reactions, reactivation of cutaneous lupus erythematosus, urticaria, anaphylactic reactions, toxic epidermal necrolysis.
Musculoskeletal and connective tissue disorders: muscle spasms, muscle weakness.
Renal and urinary disorders: renal dysfunction, interstitial nephritis.
General disorders: fever, weakness.
***** Epidemiological evidence suggests a cumulative dose-response relationship between hydrochlorothiazide and non-melanoma skin cancer.

Shelf life.
2 years.

Storage conditions.
Store in the original package at the temperature not more than 25°C.
Keep out of reach of children.

Package.
14 tablets in a blister. 2 or 6 blisters in a carton package.

Condition of supply.
By prescription.

Manufacturer.
KUSUM PHARM LLC.

Manufacturer's location and address of the place of business.
40020, Ukraine, Sumy region, Sumy, 54, Scriabina str.