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**UA/19192/01/02**

# INSTRUCTION
## for medical use

## STATORAM®-H

***Composition:***
*active substances:* lisinopril, hydrochlorothiazide;
each tablet contains lisinopril dihydrate equivalent to 10 mg lisinopril and 12.5 mg of hydrochlorothiazide, or lisinopril dihydrate equivalent to 20 mg lisinopril and 25 mg of hydrochlorothiazide;
*excipients:* mannitol (E 421), calcium hydrogen phosphate, maize starch, pregelatinized starch, silica colloidal anhydrous, magnesium stearate.

**Pharmaceutical form.** Tablets.
*Main physical and chemical properties:* white or almost white, round, biconvex tablets, smooth on both sides.

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

***Pharmacological properties.***
*Pharmacodynamics*.
Statoram®-H is a fixed-dose combination product that contains lisinopril, an inhibitor of the angiotensin-converting enzyme (ACE), and hydrochlorothiazide (HCTZ), a thiazide diuretic. Both components have modes of action and an additive hypotensive effect, which complement each other.
*Lisinopril*
Lisinopril is a peptidyl dipeptidase inhibitor. It inhibits the ACE that catalyzes the conversion of angiotensin I to angiotensin II, a vasoconstrictor peptide. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. ACE inhibition results in decreased concentrations of angiotensin II which decreases vasopressor activity and reduces aldosterone secretion. Its reduced secretion may result in an increase in the serum potassium concentration.
Lisinopril lowers blood pressure primarily by suppression of the renin-angiotensin-aldosterone system (RAAS). In addition, lisinopril is antihypertensive even in patients with low-renin hypertension. ACE is identical to kininase II, an enzyme that degrades bradykinin. It has still not been determined whether increased levels of bradykinin, a potent vasodilatory peptide, play a role in the therapeutic effects of lisinopril.
*Hydrochlorothiazide*
HCTZ is a diuretic and an antihypertensive agent. It affects the mechanism of electrolyte reabsorption by distal renal tubules 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 hypotensive effect of thiazides is unknown. Thiazides do

not usually affect normal blood pressure.
Non-melanoma skin cancer (NMSC)
Two recent pharmaco-epidemiological studies based on the data of the Danish Cancer Registry have shown a cumulative dose-dependent association between HCTZ and basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). One study included a population of 71 533 patients with BCC and 8 629 patients with SCC matched with 1 430 833 and 172 462 patients from control populations respectively. The use of high doses of HCTZ (≥ 50 000 mg cumulative) was associated with an adjusted odds ratio (OR) of 1.29 (95 % confidence interval (CI): 1.23-1.35) for BCC and 3.98 (95 % CI: 3.68-4.31) for SCC. A cumulative dose-dependent relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip cancer (SCC) were matched with 63 067 patients from control populations, using a risk-set sampling strategy. A cumulative dose-dependent relationship was demonstrated with an adjusted OR of 2.1 (95 % CI: 1.7-2.6) which increased to an OR of 3.9 (3.0-4.9) for high doses (~25 000 mg) and an OR of 7.7 (5.7-10.5) for the highest cumulative dose (~100 000 mg) (see section "Administration details").
*Pharmacokinetics.*
There is no clinically significant pharmacokinetic interaction between lisinopril and HCTZ. A combination tablet is biologically equivalent to the concomitant use of the individual components.
*Lisinopril*
Absorption
Following oral administration of lisinopril, peak serum concentrations ($C_{max}$) occur within about 7 hours, although there was a trend to a small delay in the time taken to reach $C_{max}$ in patients with acute myocardial infarction. The mean extent of absorption of lisinopril is approximately 25 %, with inter-patient variability (6–60 %) over the studied dose range (5–80 mg). The absolute bioavailability is reduced by approximately 16 % in patients with heart failure.
Lisinopril absorption is not affected by food.
Distribution
Lisinopril is not bound to serum proteins other than the circulating ACE.
Preclinical studies have established that lisinopril crosses the blood-brain barrier poorly.
Elimination
Lisinopril is not metabolized and is excreted entirely unchanged with urine. Following multiple dosing, the half-life of lisinopril is 12.6 hours. The clearance of lisinopril in healthy volunteers 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 proportionally dependent on the dose.
Hepatic impairment
Impairment of hepatic function in cirrhotic patients results in a decrease (by about 30 %) in lisinopril absorption and an increase in exposure (by approximately 50 %) compared to healthy volunteers (due to decreased clearance).
Renal impairment
Impaired renal function decreases the elimination of lisinopril, which is excreted via the kidneys, but this decrease becomes clinically important only when the glomerular filtration rate (GFR) is below 30 ml/min.
Under creatinine clearance of 30–80 ml/min, the mean area under the curve "concentration-time" (AUC) is increased only by 13 %, while, under creatinine clearance of 5–30 ml/min, a 4–5-fold increase of AUC is observed.
Lisinopril can be removed by hemodialysis. Within 4 hours of hemodialysis, plasma lisinopril concentrations decreased on average by 60 %, with a dialysis clearance within the range of 40–55 ml/min.
Heart failure
Patients with heart failure have a greater exposure of lisinopril when compared to healthy volunteers (the AUC increases on average by 125 %), however, based on the urinary recovery of

lisinopril, the absorption of the drug is reduced by approximately 16 % in patients with heart failure compared to healthy volunteers.
Elderly patients
Elderly patients have higher (approximately by 60 %) blood concentrations of lisinopril and higher AUC values compared with younger subjects.
*Hydrochlorothiazide*
Absorption
When plasma levels of HCTZ have been maintained for at least 24 hours, its plasma elimination half-life has been in the range from 5.6 to 14.8 hours.
Distribution
Hydrochlorothiazide crosses the placental barrier but does not cross the blood-brain barrier.
Elimination
At least 61 % of the HCTZ dose is eliminated unchanged within 24 hours. After oral administration, urinary excretion of HCTZ begins within 2 hours, peaks in about 4 hours and lasts 6–12 hours.

**Clinical characteristics.**
***Indications.***
The drug Statoram®-H is indicated in the treatment of mild to moderate hypertension in patients who have been stabilized on the individual components given in the same proportions.

***Contraindications.***
Hypersensitivity to active substances or excipients of the drug.
Hypersensitivity to any other ACE inhibitor.
Hypersensitivity to any sulfonamide medications.
Concomitant use with sacubitril/valsartan.
Treatment with the drug Statoram®-H may only be initiated 36 hours after the last dose of sacubitril/valsartan (see sections "Interaction with other medicinal products and other types of interaction" and "Administration details").
History of angioedema following treatment with ACE inhibitors.
Hereditary or idiopathic angioedema
Second and third trimester of pregnancy (see sections "Administration details" and "Use during pregnancy or breastfeeding").
Severe renal impairment (creatinine clearance < 30 ml/min).
Anuria.
Severe hepatic impairment.
Concomitant use of the drug Statoram®-H with aliskiren-containing medicinal products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 $m^2$) (see section "Interaction with other medicinal products and other types of interaction").

***Interaction with other medicinal products and other types of interaction.***
*Antihypertensive agents*
When combined with other antihypertensive agents, the drug Statoram®-H may decrease blood pressure. Concomitant use of nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.
The combination of lisinopril with aliskiren-containing medicines should be avoided (see sections "Contraindications" and "Administration details").
Dual blockade of RAAS through the combined use of ACE inhibitors, angiotensin II receptor blockers and aliskiren is associated with a higher frequency of adverse reactions such as hypotension, hyperkalemia, and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections "Pharmacodynamics", "Contraindications", and "Administration details").

*Drugs that may increase the risk of angioedema*
Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see sections "Contraindications" and "Administration details").
Concomitant use of ACE inhibitors with racecadotril, mammalian target of rapamycin (mTOR) inhibitors (e.g. sirolimus, everolimus, temsirolimus), or vildagliptin may lead to an increased risk of angioedema (see section "Administration details").
Concomitant administration of tissue plasminogen activators may increase the risk of angioedema.
*Lithium*
There have been reports of reversible increases in serum lithium concentrations and, accordingly, its toxicity during concomitant administration 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 not recommended, but if their concomitant use is necessary, careful monitoring of serum lithium levels should be performed as well (see section "Administration details").
*Potassium-containing supplements, potassium-sparing diuretics, potassium-containing salt substitutes, and other medicinal products that may affect serum potassium levels*
The potassium-losing effect of thiazide diuretics is usually attenuated by the potassium-sparing effect of lisinopril.
Although serum potassium usually remains within normal limits, hyperkalemia may occur in some patients treated with this medicinal product.
Potassium-sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium-containing supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Care should also be taken when the medicinal product Statoram®-H is co-administered with other medicinal products that increase serum potassium levels, such as trimethoprim and co-trimoxazole (trimethoprim/sulfamethoxazole) as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. Therefore, the combination of the medicinal product Statoram®-H with the above-mentioned drugs is not recommended. If concomitant use is necessary, they should be used with caution and with frequent monitoring of serum potassium (see section "Administration details").
*Medicinal products that can induce ventricular arrhythmias (torsades de pointes)*
Because of the increased risk of hypokalemia during concomitant administration of HCTZ and medicinal products that induce ventricular arrhythmias (e.g. antiarrhythmics, some antidepressants, and other medicinal products known to induce ventricular arrhythmias), such medicinal products should be used with caution.
*Tricyclic antidepressants/antipsychotics/anesthetics*
Concomitant use of certain anesthetics, tricyclic antidepressants, and antipsychotics with ACE inhibitors may result in further lowering of blood pressure (see section "Administration details").
*Non-steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid*
Long-term administration of NSAIDs (selective cyclooxygenase-2 inhibitors, acetylsalicylic acid (> 3 g per day), and non-selective NSAIDs) may reduce the antihypertensive and diuretic effect of ACE inhibitors and thiazide diuretics. Moreover, NSAIDs and ACE inhibitors may exert an additive effect on the increase in serum potassium levels and may lead to deterioration of renal function. These effects are usually reversible. Rarely, acute renal failure may occur, especially in patients with compromised renal function (elderly or dehydrated patients).
*Gold preparations*
Nitritoid reactions (symptoms of vasodilation including flushing, nausea, dizziness, hypotension, which can be very severe) following injectable gold preparations (for example, sodium aurothiomalate) have been reported more frequently in patients receiving treatment with ACE inhibitors.
*Sympathomimetics*
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors. Thiazides may decrease arterial responsiveness to noradrenaline, but not enough to preclude the effect of the

medicinal product that increases blood pressure.

*Antidiabetics*

Treatment with thiazide diuretics may impair glucose tolerance. This phenomenon appeared to be more likely to occur during the first 2 weeks of combined therapy and in patients with renal impairment. It may be necessary to adjust the dose of insulin or oral hypoglycemic drugs in patients with diabetes mellitus. Thiazide diuretics may increase the hypoglycemic effect of diazoxide.

*Amphotericin B (parenteral), carbenoxolone, corticosteroids, corticotropin, or laxatives*

The hypokalemic effect of HCTZ may be potentiated by drugs that affect potassium levels and hypokalemia (e.g. other kaliuretic diuretics, laxatives, amphotericin, carbenoxolone, salicylic acid derivatives).

Hypokalemia may develop during the use of steroids or adrenocorticotropic hormone (ACTH).

*Calcium salts*

Thiazide diuretics may increase serum calcium levels due to its 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 may sensitize or exaggerate the response of the heart to the toxic effects of digitalis (including increased ventricular irritability).

*Cholestyramine and colestipol*

The absorption of HCTZ is reduced by colestipol or cholestyramine. Therefore, sulfonamide diuretics should be taken at least 1 hour before or 4–6 hours after the administration of these medicinal products.

*Non-depolarizing muscle relaxants*

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

*Trimethoprim*

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

*Sotalol*

Thiazide-induced hypokalemia may increase the risk of sotalol-induced arrhythmia.

*Allopurinol*

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

*Ciclosporin*

Concomitant administration of ACE inhibitors and ciclosporin increases the risk of renal damage and hyperkalemia. Monitoring of serum potassium is recommended. Concomitant treatment with ciclosporin may increase the risk of hyperuricemia and gout-type complications.

*Heparin*

Hyperkalemia may occur during concomitant use of ACE inhibitors with heparin. Monitoring of serum potassium is recommended.

*Lovastatin*

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

*Cytostatics, immunosuppressants, procainamide*

Thiazides may reduce the renal excretion of cytotoxic agents (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects (see section “Administration details”).

*Amantadine*

Thiazides, including HCTZ, may increase the risk of adverse reactions caused by amantadine.

*Co-trimoxazole (trimethoprim/sulfamethoxazole)*

Patients taking concomitant co-trimoxazole (trimethoprim/sulfamethoxazole) may be at an increased risk of hyperkalemia (see section “Administration details”).

*Alcohol, barbiturates, or anesthetics*

Postural hypotension may become aggravated by simultaneous intake of alcohol, barbiturates, or

anesthetics.

***Administration details.***

*Non-melanoma skin cancer (NMSC)*

An increased risk of NMSC (BCC and SCC) has been observed in two epidemiological studies according to the Danish National Cancer Registry with the increase of the cumulative dose of hydrochlorothiazide. The photosensitizing effect of hydrochlorothiazide could act as a possible mechanism for the development of NMSC.

Patients taking HCTZ should be informed of the risk of NMSC, the need to regularly check their skin for new lesions, as well as to 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 used in patients to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined including histological examinations of biopsies. Moreover, the use of HCTZ may also need to be reconsidered in patients with a history of NMSC (see section "Adverse reactions").

*Symptomatic hypotension*

Symptomatic hypotension is rarely observed in patients with uncomplicated hypertension but is most likely to occur in volume-depleted patients, for example, upon diuretic therapy, dietary salt restriction, hemodialysis, diarrhea, or vomiting, or in case of severe renin-dependent hypertension (see sections "Interaction with other medicinal products and other types of interaction" and "Adverse reactions").

Regular determination of serum electrolytes should be performed in such patients. In patients at an increased risk of symptomatic hypotension, dose adjustment and treatment should be carried out under close medical supervision.

Caution should be exercised when treating patients with ischemic heart disease or cerebrovascular diseases, because an excessive decrease in blood pressure could result in a myocardial infarction or acute cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of saline. A transient hypotensive response is not a contraindication to further doses.

Following the restoration of an effective blood volume and blood pressure, reinstitution of therapy at a reduced dosage may be possible, or either of the components may be used separately 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. This effect is anticipated and does not usually require lisinopril treatment to be discontinued. If hypotension becomes symptomatic, dose reduction or discontinuation of lisinopril and hydrochlorothiazide may be necessary.

*Aortic and mitral valve stenosis/hypertrophic cardiomyopathy*

Like other ACE inhibitors, lisinopril should be given with caution to patients with mitral valve stenosis and obstruction of blood outflow from the left ventricle (for example, due to aortic stenosis or hypertrophic cardiomyopathy).

*Dual RAAS blockade*

There is evidence that the concomitant use of ACE inhibitors, angiotensin II receptor blockers, or aliskiren increases the risk of hypotension, hyperkalemia, and decreased renal function (including acute renal failure). Dual RAAS blockade through the combined use of ACE inhibitors, angiotensin II receptor blockers, or aliskiren is therefore not recommended (see sections "Interaction with other medicinal products and other types of interactions").

If the use of dual blockade is considered absolutely necessary, it should only occur under specialist supervision and under the condition of regular 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 impairment*
Thiazides are not recommended in patients with renal impairment; thiazides are ineffective at creatinine clearance values of 30 ml/min or lower (which corresponds to moderate or severe renal insufficiency).
The combination of lisinopril and HCTZ should not be prescribed to patients with renal insufficiency (creatinine clearance ≤ 80 ml/min) until the doses of individual components have been titrated to correspond to the doses present in the combination drug.
In patients with heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to further impairment of renal function. Acute renal failure (usually reversible) has been reported in some cases.
Some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney who received ACE inhibitors demonstrated an increase in serum urea and creatinine, usually reversible upon discontinuation of therapy.
This condition is especially likely to occur in patients with renal insufficiency. If renovascular hypertension is also present, there is an increased risk of severe hypotension and renal insufficiency. In such patients, treatment should be started under close medical supervision with low doses of the drug and careful dose titration. Since diuretics may contribute to the above-mentioned changes, renal function should be closely monitored during the first weeks of treatment with a combination of lisinopril and HCTZ.
Serum urea and creatinine concentrations may increase in some patients with hypertension (with no marked pre-existing renal disease) upon co-administration of lisinopril and a diuretic. This is more likely to occur in patients with a history of renal impairment. Dose reduction and (or) discontinuation of lisinopril and (or) the diuretic may be required in such cases.
*Prior diuretic therapy*
The diuretic therapy should be discontinued 2–3 days prior to the initiation of therapy with lisinopril and HCTZ. If this is not possible, treatment should be started with lisinopril monotherapy at a 5 mg dose.
*Renal transplant patients*
Since there is no experience in using the combination of lisinopril and HCTZ in renal transplant recipients, it is not recommended to prescribe the medicinal product Statoram®-H to this group of patients.
*Anaphylactoid reactions in patients receiving hemodialysis*
The use of the combination of lisinopril and HCTZ is not indicated in patients requiring hemodialysis due to renal failure.
Anaphylactoid reactions have been reported in patients receiving ACE inhibitors, undergoing certain hemodialysis procedures (for example, with high-flux AN69 membranes and during low-density lipoprotein (LDL) apheresis with dextran sulphate). In such cases, a different type of dialysis membranes or different class of antihypertensive agents should be used.
*Anaphylactoid reactions in patients undergoing LDL apheresis*
On rare occasions, patients treated with ACE inhibitors undergoing LDL apheresis with dextran sulphate demonstrated life-threatening anaphylactic reactions. Anaphylactic reactions may be avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis procedure.
*Hepatic impairment*
Thiazide diuretics 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 (see section “Contraindications”). Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice or hepatitis and progresses to fulminant liver necrosis, sometimes fatal. The mechanism of this syndrome is unclear. Patients receiving the combination of lisinopril and HCTZ who develop jaundice or marked elevation of hepatic enzymes should discontinue the drug Statoram®-H; the patient should receive appropriate medical follow-up.
*Surgery, anesthesia*

During surgery or anesthesia with agents that cause hypotension, lisinopril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, the blood volume should be corrected.

*Metabolic and endocrine system effects*

ACE inhibitor and thiazide therapy may impair glucose tolerance. Dosage adjustment of anti-diabetic agents, including insulin, may be required. In diabetic patients receiving oral anti-diabetic agents or insulin, glycemia levels should be closely monitored during the first month of treatment with an ACE inhibitor.

Latent diabetes mellitus may manifest during therapy with thiazide diuretics.

Increases in cholesterol and triglyceride levels may be associated with treatment with thiazides.

Thiazide therapy may precipitate hyperuricemia and (or) gout in some patients. However, lisinopril may increase the renal excretion of uric acid and may thus attenuate the hyperuricemic effect of HCTZ.

*Electrolyte imbalance*

Regular determination of serum electrolytes should be performed for every patient during treatment with diuretics. Thiazides, including HCTZ, can cause fluid or electrolyte imbalance (hypokalemia, hyponatremia, hypochloremic alkalosis). The signs of fluid or electrolyte imbalance include dryness of the mouth, thirst, weakness, lethargy, drowsiness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, gastrointestinal disturbances (nausea, vomiting). Hypervolemic hyponatremia may occur in patients prone to edemas in hot weather. Chloride deficiency is generally mild and does not require treatment. Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion and may cause a slight periodic elevation of serum calcium levels. Marked hypercalcemia may be indicative of hidden hyperparathyroidism. Thiazide diuretics should be discontinued before carrying out tests for parathyroid function.

*Hyperkalemia*

ACE inhibitors can cause hyperkalemia because they inhibit the release of aldosterone. This effect is usually insignificant in patients with normal renal function. However, in patients with impaired renal function, type 2 diabetes mellitus, and/or in patients taking potassium-containing supplements (including salt substitutes), potassium-sparing diuretics, as well as in patients taking medicinal products that can increase serum potassium levels (e.g. heparin, trimethoprim, or combined medicinal product co-trimoxazole, also known as trimethoprim/sulfamethoxazole, and, in particular, aldosterone antagonists or angiotensin-receptor blockers), hyperkalemia can occur. Serum potassium levels and renal function should be regularly monitored if concomitant use of these drugs is required (see section “Interaction with other medicinal products and other types of interaction”).

*Patients with diabetes mellitus*

In diabetic patients treated with oral anti-diabetic agents or insulin, glycemic levels should be closely monitored during the first month of treatment with an ACE inhibitor (see section “Interaction with other medicinal products and other types of interaction”).

*Hypersensitivity, angioedema*

There have been isolated reports of angioedema of the face, extremities, lips, tongue, glottis, and (or) larynx at any point of therapy with ACE inhibitors, including lisinopril. Angioedema may occur at any time during therapy.

If such reaction occurs, lisinopril should be discontinued immediately; the patient should receive appropriate treatment and be monitored until complete disappearance of symptoms.

Even if the edema only involves the tongue (without respiratory disturbances), the patient should be monitored for a prolonged period of time since treatment with antihistamines and corticosteroids may be ineffective.

In rare cases, angioedema of the larynx or tongue can lead to death. Edema of the tongue, glottis, or larynx may lead to airway obstruction, especially in patients with a history of airway surgery. Emergency therapy should be administered in such cases. Administration of adrenaline solution

and (or) the maintenance of airway patency may be required. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.
The incidence of ACE inhibitor-induced angioedema is greater in negroid patients than in patients of other races.
Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at an increased risk of angioedema as a response to the use of ACE inhibitors (see section "Contraindications").
Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema. Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of lisinopril. Treatment with lisinopril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections "Contraindications" and "Interaction with other medicinal products and other types of interaction").
Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk of angioedema (e.g. edema of the airways or tongue, with or without respiratory impairment) (see section "Interaction with other medicinal products and other types of interaction").
Caution should be exercised when starting racecadotril, mTOR inhibitors and vildagliptin in patients already taking and ACE inhibitor.
*Thiazides*
Hypersensitivity reactions may occur in patients receiving thiazides with or without history of allergy or bronchial asthma. Activation or exacerbation of systemic lupus erythematosus has been reported with the use of thiazide diuretics.
*Desensitization*
Patients receiving ACE inhibitors may develop anaphylactoid reactions during desensitization treatment (e.g. to hymenoptera venom). These reactions may be avoided by temporarily withholding ACE inhibitors, however, adverse reactions may reappear upon inadvertent rechallenge of the drug.
*Neutropenia/agranulocytosis*
Neutropenia (agranulocytosis), thrombocytopenia, and anemia have been reported in patients receiving ACE inhibitors. Neutropenia occurs rarely in patients with normal renal function and no other complicating factors. Neutropenia and agranulocytosis are reversible after discontinuation of ACE inhibitors. Lisinopril should be used with extreme caution in patients with collagen vascular disease, those receiving immunosuppressant therapy, treatment with allopurinol or procainamide, or those with a combination of these complicating factors, especially in patients with pre-existing renal impairment. Sometimes this category of patients developed serious infections, including those not responding to intensive antibiotic therapy. If lisinopril is used in such patients, periodic monitoring of white blood cell counts is advised. Patients should be instructed to report any signs of infection.
*Ethnicity*
The incidence of angioedema during the use of ACE inhibitors is greater in negroid patients compared with patients of other races.
As with other ACE inhibitors, lisinopril is less effective in lowering blood pressure in negroid patients compared to patients of other races. This may be associated with mainly low renin in hypertensive negroid patients.
*Cough*
Cough may develop with the use of ACE inhibitors. This 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 preparations*
The combination of ACE inhibitors and lithium preparations is usually not recommended (see section "Interaction with other medicinal products and other types of interaction").
*Anti-doping test*

The medicinal product Statoram®-H contains HCTZ which may produce false-positive results in anti-doping tests.

*Pregnancy*

ACE inhibitors should not be initiated during pregnancy. As long continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive 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 breastfeeding").

*Acute respiratory toxicity*

Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking HCTZ. Pulmonary edema typically develops within minutes to hours after HCTZ intake. At the onset, symptoms include dyspnea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, Statoram®-H should be withdrawn and appropriate treatment given. The drug Statoram®-H should not be administered to patients who previously experienced ARDS following HCTZ intake.

*Choroidal effusion, acute myopia and secondary angle-closure glaucoma*

Sulfonamide or sulfonamide derivative drugs may cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, 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 drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake 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 sulfonamide or penicillin allergy.

*Use during pregnancy or breastfeeding.*

*Pregnancy*

ACE inhibitors

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| The use of ACE inhibitors is not recommended during the I trimester of pregnancy (see section "Administration details"). The use of ACE inhibitors is contraindicated in the II and III trimesters of pregnancy (see sections "Contraindications" and "Administration details"). |

The existing data regarding the risk of teratogenicity following exposure to ACE inhibitors during the I trimester of pregnancy has not been conclusive, however, a small increase in risk cannot be ruled out.

So long as continued ACE inhibitor therapy is considered necessary, patients planning pregnancy should be changed to alternative anti-hypertensive therapy which includes agents that have an established safety profile for use during pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if possible, alternative therapy should be initiated.

The use of ACE inhibitors during the II and III trimesters of pregnancy is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalemia).

If ACE inhibitors have been used during the III trimester of pregnancy, ultrasound monitoring of renal function and the skull is recommended. Infants whose mothers have received ACE inhibitors should be closely observed for potential hypotension (see sections "Contraindications" and "Administration details").

Hydrochlorothiazide

The experience of using HCTZ during pregnancy, in particular during the I trimester, is limited. Data from animal studies is insufficient.

HCTZ crosses the placenta. The pharmacological mechanism of action of HCTZ indicates that its use during the II and III trimesters of pregnancy may compromise feto-placental perfusion and

may cause fetal and neonatal effects like jaundice, disturbance of the electrolyte balance, and thrombocytopenia.
HCTZ should not be used for the treatment of edema, hypertension, or preeclampsia in pregnant patients due to the risk of decreased plasma volume and reduced utero-placental perfusion, instead of a beneficial effect on the course of the disease.
HCTZ should not be used for the treatment of essential hypertension in pregnant women except in rare cases where no alternative medicinal products can be used.
*Breastfeeding*
ACE inhibitors
Since no information is available regarding the use of lisinopril/hydrochlorothiazide during breastfeeding, lisinopril/hydrochlorothiazide is not recommended, and alternative treatments with known safety profiles should be used, especially while nursing a newborn or preterm infant.
Hydrochlorothiazide
HCTZ is excreted in human milk in small amounts. Thiazides in high doses may increase diuresis, which may inhibit breastmilk production.
The use of lisinopril/HCTZ during breastfeeding is contraindicated. If alternative treatment is impossible during breastfeeding, lisinopril/HCTZ doses should be prescribed as low as possible.

*Effect on reaction rate when driving motor transport or using other mechanisms.*
As with other antihypertensive agents, lisinopril/HCTZ may have a mild to moderate effect on the ability to drive motor transport or use other mechanisms. The risk is greater at the start of the treatment or when the dose is modified, as well as when the combined drug is used with alcohol, however, these effects depend on the patient's susceptibility.
Possible dizziness and tiredness when driving motor transport or using other mechanisms should be taken into account.

***Dosage and administration.***
Essential hypertension
The usual dose is 1 tablet 1 time a day. The drug Statoram®-H should be taken at approximately the same time each day. If the desired therapeutic effect cannot be achieved within 2–4 weeks, the dose can be increased to 2 tablets 1 time a day.
Renal impairment
Thiazides should not be used in patients with renal impairment, they are ineffective in moderate or severe renal insufficiency (creatinine clearance ≤ 30 ml/min).
The medicinal product Statoram®-H should not be used as initial therapy in patients with renal insufficiency.
In patients with creatinine clearance of > 30 and < 80 ml/min, the medicinal product Statoram®-H may be used only after dose titration of the individual components. The recommended initial dose for lisinopril monotherapy in such patients is 5–10 mg.
Prior diuretic therapy
Symptomatic hypotension may occur following the initial dose of the drug Statoram®-H. This is more likely in dehydrated patients (e.g. as a result of diuretic therapy). The diuretic therapy should be discontinued 2–3 days prior to the initiation of therapy with the medicinal product Statoram®-H. If this is not possible, treatment should be started with lisinopril alone, at a dose of 5 mg.
Elderly patients
Dose adjustment is not required.
No age-related changes in the efficacy or tolerability of the drug have been determined during the use of lisinopril/HCTZ.
Lisinopril, within a daily dosage range of 20–80 mg, was equally effective in the elderly (65 years old or over) and middle-aged patients. Monotherapy with lisinopril was as effective in reducing diastolic arterial blood pressure as monotherapy with HCTZ or atenolol. Age did not affect the tolerability of lisinopril.

*Children.*
The safety and effectiveness of using the lisinopril/HCTZ combination in children have not been established.

***Overdose.***
*Symptoms*
Limited data are available for overdose in humans.
The most likely symptoms of overdosage of ACE inhibitors are: hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, cough.
Additionally, there may be symptoms of HCTZ overdose: increased diuresis, depression of consciousness (including coma), convulsions, paresis, arrhythmia, renal failure.
In the event of concomitant use of digitalis drugs, hypokalemia may occur, which increases the risk of arrhythmia.
*Treatment*
The recommended treatment of overdose is intravenous infusion of saline solution. If severe hypotension occurs, the patient should be placed in the supine position. Treatment with angiotensin II infusion (if available) 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 hemodialysis (see section "Pharmacological properties"). Fitting a pacemaker is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored frequently.
Bradycardia or excessive vagal reactions can also be reduced by taking atropine.

***Adverse reactions.***
Adverse reactions reported during treatment with lisinopril and/or HCTZ are listed below by organ systems and frequency: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10000, <1/1000), very rare (<1/10000, including isolated cases), frequency unknown (frequency cannot be estimated from the available data).
The following adverse reactions were most frequently observed with lisinopril and/or HCTZ: cough, dizziness, hypotension, and headache.
Lisinopril
*Blood and lymphatic system disorders:* rare – decreases in hemoglobin, decreases in hematocrit; very rare – bone marrow depression, anemia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis (see section "Administration details"), hemolytic anemia, lymphadenopathy, autoimmune disease.
*Immune system disorders:* frequency unknown – anaphylactic/anaphylactoid reactions.
*Endocrine disorders:* rare – syndrome of inappropriate antidiuretic hormone secretion (SIADH).
*Metabolism and nutrition disorders:* very rare – hypoglycemia.
*Nervous system disorders:* common – dizziness, headache, syncope; uncommon – paresthesia, vertigo, taste disturbance, sleep disturbance; rare – olfactory disturbance.
*Psychiatric disorders:* uncommon – mood alterations, depression; rare – mental confusion; frequency unknown – hallucinations.
*Cardiovascular disorders:* common – hypotension (including orthostatic); uncommon – myocardial infarction or cerebrovascular accident secondary to excessive hypotension in high-risk patients (see section "Administration details"), palpitations, tachycardia, Raynaud's syndrome; frequency unknown – hot flushes.
*Respiratory, thoracic and mediastinal disorders:* common – cough (see section "Administration details"); uncommon – rhinitis; very rare – bronchospasm, sinusitis, allergic alveolitis/eosinophilic pneumonia

*Gastrointestinal disorders:* common – diarrhea, vomiting; uncommon – nausea, abdominal pain, dyspepsia; rare – dry mouth; very rare – pancreatitis, intestinal angioedema.
*Hepatobiliary disorders:* uncommon – increases in liver enzymes and in serum bilirubin; very rare – hepatitis (hepatocellular or cholestatic), jaundice, hepatic failure (see section "Administration details")*.
*Skin and subcutaneous tissue disorders:* uncommon – rash, pruritus; rare – hypersensitivity/angioedema (face, extremities, lips, tongue, glottis, and/or larynx) (see section "Administration details"), urticaria, alopecia, psoriasis; very rare – excessive sweating, pemphigus, severe skin disorders (pemphigus, toxic epidermal necrolysis, Stevens–Johnson syndrome, erythema multiforme, cutaneous pseudolymphoma**).
*Urogenital disorders:* common – renal dysfunction; rare – uremia, acute renal failure; very rare – oliguria/anuria.
*Reproductive system and breast disorders:* uncommon – impotence; rare – gynecomastia.
*General disorders:* uncommon – fatigue, asthenia.
*Laboratory investigations:* uncommon – increases in blood urea, increases in serum creatinine, hyperkalemia; rare – hyponatremia.
*There have been very rare reports of patients who developed liver failure caused by hepatitis. Patients who developed jaundice or a significant elevation of liver enzymes associated with treatment should discontinue the drug and undergo appropriate medical examination.
**A symptom complex has been reported which may include one or more of the following: fever, vasculitis, myalgia, arthralgia/arthritis, positive antinuclear antibodies (ANA), elevated erythrocyte sedimentation rate (ESR), eosinophilia and leucocytosis, rash, photosensitivity, or other dermatological manifestations.
Hydrochlorothiazide
*Infections and invasions:* frequency unknown – sialadenitis.
*Benign, malignant and unspecified neoplasms, including cysts and polyps:* frequency unknown – NMSC (basal cell carcinoma and squamous cell skin cancer).
*Blood and lymphatic system disorders:* frequency unknown – leucopenia, neutropenia/agranulocytosis, thrombocytopenia, aplastic anemia, hemolytic anemia, bone marrow depression.
*Metabolism and nutrition disorders:* frequency unknown – anorexia, hyperglycemia, glucosuria, hyperuricemia, electrolyte imbalance (including hyponatremia, hypokalemia, hypochloremic alkalosis, hypomagnesemia), increased cholesterol and triglyceride levels, gout.
*Psychiatric disorders*: frequency unknown – anxiety, depression, sleep disturbance.
*Nervous system disorders:* frequency unknown – loss of appetite, paresthesia, dizziness.
*Eye disorders:* frequency unknown – xanthopsia, temporary visual disturbances, acute myopia, acute angle-closure glaucoma, choroidal effusion.
*Ear and labyrinth disorders:* frequency unknown – vertigo.
*Cardiovascular disorders:* frequency unknown – orthostatic hypotension, necrotizing angiitis (vasculitis, cutaneous vasculitis).
*Respiratory, thoracic and mediastinal disorders*: very rare – acute respiratory distress syndrome (ARDS) (see section "Administration details"); frequency unknown – respiratory distress syndrome, including pneumonitis and pulmonary edema.
*Gastrointestinal disorders*: frequency unknown – irritation of the mucous lining of the stomach, diarrhea, constipation, pancreatitis.
*Hepatobiliary disorders:* frequency unknown – jaundice (intrahepatic cholestatic jaundice).
*Skin and subcutaneous tissue disorders:* frequency unknown – photosensitivity reactions, rash, systemic lupus erythematosus, lupus-like cutaneous reactions, re-activation of cutaneous manifestations of systemic lupus erythematosus, urticaria, anaphylactic reactions, toxic epidermal necrolysis.
*Musculoskeletal and connective tissue disorders*: frequency unknown – muscle spasms, muscle weakness.
*Urogenital disorders:* frequency unknown – renal dysfunction, interstitial nephritis.
*General disorders:* fever, weakness.

Description of selected adverse reactions
Non-melanoma skin cancer (NMSC): based on available data from epidemiological studies, a cumulative dose-dependent association between HCTZ and NMSC has been observed (see section "Pharmacokinetic properties" and "Administration details").
Reporting of adverse reactions
Reporting adverse reactions after the registration of the medicinal product is of great importance. It allows to monitor the correlation of the benefits and risks related to the use of the medicinal product. Healthcare and pharmaceutical professionals, as well as patients or their legal representatives are asked to report any suspected adverse reactions and lack of efficacy of the medicinal product through the Automated pharmacovigilance information system available at: https://aisf.dec.gov.ua.

***Shelf life.***
For dosage of 10 mg/12.5 mg: 3 years.
For dosage of 20 mg/25 mg: 2 years.

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

**Package.**
*For dosage of 10 mg/12.5 mg*:
14 tablets are in a blister. 2 or 6 blisters are in a carton box.
10 tablets are in a blister. 3 or 6 blisters are in a carton box.
*For dosage of 20 mg/25 mg*:
10 tablets are in a blister. 3 or 6 blisters are in a carton box.

**Conditions of supply.**
By prescription.

**Manufacturer.**
LLC "KUSUM PHARM".

**Address of manufacturer and manufacturing site.**
40020, Ukraine, Sumy region, Sumy, Skryabina Str., 54.

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