

**INSTRUCTION
for medical use**

STATORAM®-H

Composition:

active substances: lisinopril, hydrochlorothiazide;

1 tablet contains lisinopril dihydrate equivalent to lisinopril 20 mg and hydrochlorothiazide 12.5 mg;

excipients: mannitol (E 421), calcium hydrogen phosphate, maize starch, pregelatinized starch, silica colloidal anhydrous, magnesium stearate.

Pharmaceutical form. Tablets.

Basic physico-chemical properties: round flat white or off-white tablets with an embossing “K” on one side and smooth on the other side.

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

Pharmacological properties.

Pharmacodynamics.

Satoram®-H is a fixed-dose combined drug which contains lisinopril, an angiotensin-converting enzyme (ACE) inhibitor, 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 ACE, which catalyzes the conversion of angiotensin I to angiotensin II, a vasoconstrictive peptide. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in a decreased angiotensin II concentration, which reduces the vasoconstrictive activity and aldosterone secretion. Its reduced secretion may lead to increased serum potassium concentrations.

Lisinopril lowers blood pressure primarily by suppressing the renin-angiotensin-aldosterone system (RAAS). At the same time, lisinopril is an antihypertensive agent even in patients with low-renin hypertension. ACE is identical to kininase II, an enzyme that facilitates the degradation of bradykinin. Whether increased levels of bradykinin, a potent vasodilating peptide, play a certain role in the therapeutic effects of lisinopril remains unclear.

Hydrochlorothiazide

HCTZ is a diuretic and antihypertensive agent. It affects the mechanism of electrolyte reabsorption in 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)

The results of two pharmacoepidemiologic studies based on the data from 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 the population of 71 533 patients with BCC and 8 629 patients with SCC compared to 1 430 833 and 172 462 patients from the control population respectively. The use of high-dose HCTZ ($\geq 50\,000$ 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 distinct cumulative dose-dependent association was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and the use of HCTZ: 633 cases of lip cancer (SCC) were compared to 63 067 patients from the control population using a risk-set sampling strategy. A cumulative dose-dependent relation 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 ($\sim 25\,000$ mg) and an OR of 7.7 (5.7-10.5) for the highest cumulative dose ($\sim 100\,000$ mg) (see section “Administration details”).

Pharmacokinetics.

There is no clinically significant pharmacokinetic interaction between lisinopril and HCTZ. A combination tablet is bioequivalent to the concomitant use of the individual components.

Lisinopril

Absorption

After oral administration, the peak serum concentration (C_{\max}) of lisinopril is reached approximately within 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 lisinopril absorption is approximately 25 % with inter-subject variability (6–60 %) over all studied doses (5–80 mg). The absolute bioavailability is reduced by approximately 16 % in patients with heart failure.

Food intake does not affect the absorption of lisinopril.

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 as is excreted entirely unchanged with urine. After multiple dosing the elimination half-life of lisinopril is 12.6 hours. The clearance of lisinopril in healthy volunteers is approximately 50 ml/min. Decreased 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

Hepatic impairment in patients with cirrhosis results in reduced (approximately by 30 %) absorption of lisinopril and its increased (approximately by 50 %) exposure compared to healthy volunteers (due to decreased clearance).

Renal impairment

Renal impairment decreases the elimination of lisinopril, which is excreted by kidneys, but such a decrease becomes clinically significant 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 a 4–5-fold increase of AUC is observed under creatinine clearance of 5–30 ml/min.

Lisinopril can be removed by hemodialysis. Within 4 hours of hemodialysis, plasma lisinopril concentrations decreased on average by 60 %, and the dialysis clearance ranged between 40–55 ml/min.

Heart failure

Patients with heart failure have greater exposure to lisinopril compared to healthy volunteers (AUC increases on average by 125 %), however, based on the data on excretion of lisinopril with urine, 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 AUC values compared to younger patients.

Hydrochlorothiazide

Absorption

When plasma levels of HCTZ have been maintained for at least 24 hours, its plasma elimination half-life ranged from 5.6 to 14.8 hours.

Distribution

Hydrochlorothiazide crosses the placental barrier and does not cross the blood-brain barrier.

Elimination

At least 61 % of the HCTZ dose is excreted unchanged within 24 hours. After oral administration, the excretion of HCTZ with urine begins within 2 hours, reaches its peak in about 4 hours and lasts 6–12 hours.

Clinical characteristics.

Indications.

The drug Statoram[®]-H is indicated for the treatment of mild or moderate hypertension in patients who have been stabilized on the individual components in the same proportions.

Contraindications.

Hypersensitivity to active substances or excipients of the drug.

Hypersensitivity to any other ACE inhibitor.

Hypersensitivity to any sulfonamide agents.

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 forms of interaction” and “Administration details”).

History of angioedema associated with previous treatment with ACE inhibitors.

Hereditary or idiopathic angioedema.

The second and third trimesters 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 agents is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m²) (see section “Interaction with other medicinal products and other forms of interaction”).

Interaction with other medicinal products and other forms 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 decrease blood pressure.

The combination of lisinopril with aliskiren-containing agents should be avoided (see sections “Contraindications” and “Administration details”).

Dual RAAS blockade through the combined use of ACE inhibitors, angiotensin II receptor blockers and aliskiren is associated with 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. with sirolimus, everolimus, temsirolimus) or vildagliptin may result in an increased risk of angioedema (see section “Administration details”).

Concomitant treatment with tissue-type 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 use with ACE inhibitors. Diuretic agents and ACE inhibitors decrease the renal clearance of lithium and pose a high risk of lithium toxicity. The combination of lisinopril and hydrochlorothiazide with lithium is not recommended; if their concomitant use is required, serum lithium levels should also be carefully monitored (see section “Administration details”).

Potassium-containing supplements, potassium-sparing diuretics or potassium-containing salt substitutes, and other drugs 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 levels usually remain within normal limits, hyperkalemia may occur in some patients using this drug.

Potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium-containing supplements, or potassium-containing salt substitutes may result in significantly increased serum potassium levels. Caution should also be exercised when co-administering the drug Satoram®-H with other agents 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 drug Satoram®-H with the above-mentioned agents is not recommended. If concomitant use is required, they should be used with caution and with frequent monitoring of serum potassium levels (see section “Administration details”).

Medicinal products that can induce ventricular arrhythmias (torsades de pointes)

Due to the increased risk of hypokalemia during the concomitant use of HCTZ with drugs inducing ventricular arrhythmias (e.g. antiarrhythmics, some antidepressants, and other drugs that may induce ventricular arrhythmias), such drugs should be used with caution.

Tricyclic antidepressants/antipsychotics/anesthetics

Concomitant use of some anesthetics, tricyclic antidepressants, and antipsychotics with ACE inhibitors may further result in low blood pressure (see section “Administration details”).

Non-steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid

Long-term use of NSAIDs (selective cyclooxygenase-2 inhibitors, acetylsalicylic acid (> 3 g per day) and non-selective NSAIDs) may reduce antihypertensive and diuretic effects of ACE inhibitors and thiazide diuretics. Moreover, NSAIDs and ACE inhibitors may have an additive effect on the increase in serum potassium levels and may lead to renal impairment. These effects are usually reversible. Acute renal failure may rarely occur, especially in patients with renal impairment (elderly or dehydrated patients).

Gold preparations

Nitritoid reactions (symptoms of vasodilation including flushing, nausea, dizziness, hypotension, which can be very severe) after injections of gold preparations (e.g. sodium aurothiomalate) have been reported more frequently in patients receiving treatment with ACE inhibitors.

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effect of ACE inhibitors. Thiazides may decrease arterial responsiveness to noradrenaline, but insufficiently to preclude the effect of the drug that increases blood pressure.

Antidiabetics

Treatment with thiazide diuretics may impair glucose tolerance. This phenomenon is more likely to occur during the first 2 weeks of combination therapy and in patients with renal impairment.

Dose adjustment of insulin or oral hypoglycemic drugs may be required 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 enhanced by drugs affecting potassium levels and hypokalemia (e.g. other kaliuretic diuretics, laxatives, amphotericin, carbenoxolone, salicylic acid derivatives).

Hypokalemia may develop during concomitant use of steroids or adrenocorticotrophic hormone (ACTH).

Calcium salts

Thiazide diuretics may increase serum calcium levels due to its decreased excretion. If calcium supplements or vitamin D should be prescribed, serum calcium levels should be monitored and the dose should be adjusted accordingly.

Cardiac glycosides

Hypokalemia may sensitize or exaggerate the response of the heart to the toxic effects caused by digitalis drugs (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. tubocurarine).

Trimethoprim

Concomitant use 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 use of ACE inhibitors with allopurinol increases the risk of renal damage which may result in an increased risk of leucopenia.

Ciclosporin

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

Heparin

Concomitant use of ACE inhibitors with heparin may cause hyperkalemia. Monitoring of serum potassium levels is recommended.

Lovastatin

Concomitant use of ACE inhibitors with lovastatin increases the risk of hyperkalemia.

Cytostatics, immunosuppressants, procainamide

Thiazides may reduce the renal excretion of cytotoxic medicinal products (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 be 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 may be a possible mechanism for NMSC.

Patients taking HCTZ should be informed of the risk of NMSC, about the necessity to regularly check their skin for any new lesions, and to immediately report any suspicious skin lesions. Preventive measures, particularly limited exposure to sunlight and UV rays and adequate protection in case of exposure, should be recommended to 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 should 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, however, the risk of low blood pressure is most likely to occur in patients with decreased volume of circulating blood, e.g. 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 forms of interaction” and “Adverse reactions”).

Serum electrolyte levels should be regularly monitored in such patients. Dose titration and treatment of patients with an increased risk of clinically significant hypotension are initiated under close medical supervision.

The drug should be used with particular caution in patients with ischemic heart disease or cerebrovascular diseases because excessively low blood pressure may result in myocardial infarction or acute cerebrovascular accident.

If arterial hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of saline solution. Transient hypotension is not a contraindication for further doses.

Following the restoration of an effective blood volume and the normalization of blood pressure, therapy may be re-initiated at lower doses, or either of the components may be used separately.

Lowering of systemic blood pressure may occur with lisinopril in some patients with heart failure who have normal or low blood pressure. This effect is anticipated and does not usually require treatment with drug to be discontinued. If clinically significant hypotension occurs, dose reduction or discontinuation of lisinopril and hydrochlorothiazide may be required.

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy

Like other ACE inhibitors, lisinopril should be used with caution in 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 section “Interaction with other medicinal products and other forms of interaction”).

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 \leq 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 result in further renal impairment. 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 more 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 initiated 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 the combination of 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 patients, it is not recommended to prescribe the drug 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 (e.g. 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

In rare cases, 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 hepatic impairment or progressive liver disease, since minor alterations of fluid and electrolyte balance may cause 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 with a fatal outcome. The mechanism of this syndrome is unclear. If patients receiving the combination of lisinopril and HCTZ develop jaundice or marked elevation of hepatic enzymes, the drug Statoram[®]-H should be discontinued; the patient should be under close medical supervision.

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 become 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 pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, gastrointestinal disorders (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 are known 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, hyperkalemia may occur 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). 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 forms 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 forms of interaction”).

Hypersensitivity, angioedema

Angioedema of the face, extremities, lips, tongue, glottis, and (or) larynx may rarely occur 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 under medical supervision until complete disappearance of symptoms.

Even if the edema only involves the tongue (without respiratory disorders), 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 may lead to a fatal outcome. Edema of the tongue, glottis, or larynx may lead to airway obstruction, especially in patients with a history of airway surgery. Emergency therapy is indicated 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.

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 should not be initiated earlier than 36 hours after the last dose of lisinopril. Treatment with lisinopril should 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 forms of interaction”).

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may result in 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 forms of interaction”).

Caution should be exercised when initiating treatment with racecadotril, mTOR inhibitors and vildagliptin in patients already taking an 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 discontinuing ACE inhibitors, however, adverse reactions may reappear upon inadvertent repeated use 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 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 arterial 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 forms of interaction”).

Anti-doping test

The drug Satoram®-H contains HCTZ which may produce false-positive results in anti-doping tests.

Pregnancy

ACE inhibitors should not be initiated during pregnancy. As long as 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 discontinued immediately, and, if appropriate, alternative therapy should be initiated (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 usually 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, the drug Statoram[®]-H should be discontinued and appropriate treatment should be given. The drug Statoram[®]-H should not be prescribed 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 usually occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma may 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

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 discontinued 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 exposure to ACE inhibitor has occurred during the III trimester of pregnancy, ultrasound monitoring of renal function and 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, arterial 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

Because no information is available regarding the use of lisinopril/hydrochlorothiazide during breastfeeding, lisinopril/hydrochlorothiazide is not recommended, alternative treatments with the established safety profiles should be preferred, 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 fatigue 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 drug 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 drug 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 arterial 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 drug 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 (over 65 years) 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, measures aimed at eliminating lisinopril (e.g. emesis, gastric lavage, administration of absorbents and sodium sulphate) should be taken. 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 may 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 ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1000$, $< 1/100$), rare ($\geq 1/10000$, $< 1/1000$), 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 – flushing.

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 balance 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. 3 years.

Storage conditions.

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

Package.

10 tablets are in a blister. 3 or 6 blisters are in a carton box.
14 tablets are in a blister. 2 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.

or

Manufacturer.

LLC “GLADPHARM LLC”.

Address of manufacturer and manufacturing site.

40020, Ukraine, Sumy region, Sumy, Davydovskoho Hryhoriia Str., 54.

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