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INSTRUCTION
for medical use

PRAMILET®

Composition:
active substance: amlodipine, lisinopril;
5 mg/10 mg tablets: each tablet contains amlodipine besylate equivalent to 5 mg amlodipine and lisinopril dihydrate equivalent to 10 mg lisinopril;
5 mg/20 mg tablets: each tablet contains amlodipine besylate equivalent to 5 mg amlodipine and lisinopril dihydrate equivalent to 20 mg lisinopril;
10 mg/20 mg tablets: each tablet contains amlodipine besylate equivalent to 10 mg amlodipine and lisinopril dihydrate equivalent to 20 mg lisinopril;
excipients: microcrystalline cellulose, sodium starch glycolate (type A), silica colloidal anhydrous, magnesium stearate.

Pharmaceutical form. Tablets.
Main physico-chemical properties:
for 5 mg/10 mg dosage: white or off-white, round, flat tablets with an embossing "K" on one side and smooth on the other side;
for 5 mg/20 mg dosage: white or off-white, round, flat tablets with an embossing "5" and "20", divided with a score line on one side and smooth on the other side;
for 10 mg/20 mg dosage: white or off-white, round, flat tablets with an embossing "10" and "20", divided with a score line on one side and smooth on the other side.

Pharmacotherapeutic group. Combinations of angiotensin-converting enzyme (ACE) inhibitors. ACE inhibitors in combination with calcium antagonists. Lisinopril and amlodipine. ATC code C09B B03.

Pharmacological properties
Pramilet® is a fixed-dose combination containing the active substances lisinopril and amlodipine.
Lisinopril
Lisinopril is a peptidyl dipeptidase inhibitor. It inhibits the angiotensin-converting enzyme (ACE) that catalyzes the conversion of angiotensin I to the vasoconstrictor peptide angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased concentrations of angiotensin II and, consequently, decreased vasopressor activity and reduced aldosterone secretion. Reduction of the latter may result in elevations in serum potassium levels.

Whilst the mechanism through which lisinopril lowers blood pressure lies in the suppression of the renin-angiotensin-aldosterone system, lisinopril is antihypertensive even in patients with low renin hypertension. ACE is identical to kininase II, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodilatory peptide, play a role in the therapeutic effects of lisinopril remains to be elucidated.

Amlodipine

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) which inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

The mechanism of the hypotensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle.

The reduction of the total ischemic burden occurs through two mechanisms of action:

- Amlodipine dilates peripheral arterioles and thus reduces the total peripheral vascular resistance (afterload). Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.
- The mechanism of action of amlodipine also probably involves the dilatation of coronary arteries and coronary arterioles, both in normal and ischemic regions of the myocardium. This increases myocardial oxygen delivery in patients with vasospastic angina (Prinzmetal or variant angina).

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the standing and supine positions throughout the 24 hour interval. Due to the slow onset of action, rapid hypotensive effect is not obtained.

In patients with angina, once daily administration of amlodipine increases exercise capacity, time to angina onset and time to 1 mm ST segment depression, as well as decreases both the frequency of angina attacks and glyceryl trinitrate tablet consumption.

Amlodipine does not have any adverse effects on the metabolism or plasma lipid concentrations and is suitable for the treatment of patients with asthma, type 2 diabetes and gout.

Pharmacokinetics.

Lisinopril

Lisinopril is a non-sulphydryl-containing ACE inhibitor for oral use.

Absorption

Following oral administration of lisinopril, peak serum concentrations occur within about 7 hours, although there was a trend to a small delay in the time taken to reach peak serum concentrations in patients with acute myocardial infarction. Based on urinary recovery, the mean extent of absorption of lisinopril is approximately 25 % with interpatient variability of 6 % to 60 % over the dose range studied (5 to 80 mg). The absolute bioavailability is reduced to approximately 16 % in patients with heart failure. Lisinopril absorption is not affected by the presence of food.

Distribution

Lisinopril does not bind to serum proteins other than to the circulating ACE. Pre-clinical studies indicate that lisinopril crosses the blood-brain barrier poorly.

Elimination

Lisinopril does not undergo metabolism and is excreted entirely unchanged into the urine. Upon multiple dosing, lisinopril has an effective elimination half-life of 12.6 hours. The renal clearance of lisinopril in healthy subjects is approximately 50 ml/min. Serum lisinopril concentrations decline with a prolonged elimination half-life phase which does not contribute to drug accumulation. This terminal phase probably represents saturable binding to ACE and is not proportional to the dose.

Pharmacokinetic properties in special patient groups

Hepatic impairment

Impairment of the hepatic function in cirrhotic patients resulted in a decrease in lisinopril absorption (by about 30 % as determined by urinary recovery), however, the exposure increased (by approximately 50 %) compared to that in healthy subjects 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 is below 30 ml/min. In mild to moderate renal impairment (creatinine clearance from 30 to 80 ml/min), the mean area under the "concentration – time" curve (AUC) was increased by 13 % only, while a 4.5-fold increase in the mean AUC was observed in severe renal impairment (creatinine clearance from 5 to 30 ml/min). Lisinopril can be removed by dialysis. After 4 hours of hemodialysis, plasma lisinopril concentrations decreased on average by 60 %, with a dialysis clearance between 40 and 55 ml/min.

Heart failure

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

Elderly patients

Elderly patients have elevated blood lisinopril concentrations and higher AUC values (by approximately 60 %) compared with younger subjects.

Amlodipine

Absorption, distribution, binding to plasma proteins

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood concentrations reached between 6–12 hours following the administration. Absolute bioavailability has been estimated to be between 64 and 80 %. The volume of distribution is approximately 21 l/kg. In *vitro studies* have shown that approximately 97.5 % of circulating amlodipine is bound to plasma proteins.

The bioavailability of amlodipine is not affected by food intake.

Biotransformation and elimination

The terminal plasma elimination half-life is about 35–50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolized by the liver to inactive metabolites with 10 % of the parent compound and 60 % of metabolites excreted in the urine.

Pharmacokinetic properties in special patient groups

Hepatic impairment

Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer elimination half-life and an increase in AUC of approximately 40–60%.

Elderly patients

The time to reach peak plasma concentrations of the drug is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in the AUC and elimination half-life in elderly patients.

Increases in the AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.

Fixed-dose combination

No pharmacokinetic interactions have been described between the active substances of the drug Pramilet®, tablets. Pharmacokinetic parameters (AUC, C_{max}, t_{max}, $t_{1/2}$) were not different from those observed after administration of the individual components separately.

Food intake does not affect the gastrointestinal intake of the drug Pramilet®, tablets.

Clinical characteristics.

Indications.

Essential hypertension in adults.
Pramilet® is used in patients with blood pressure adequately controlled with concurrent lisinopril and amlodipine in the respective doses.

Contraindications.
Associated with lisinopril:
- hypersensitivity to lisinopril or to any other ACE inhibitor;
- history of angioedema associated with previous ACE inhibitor therapy;
- hereditary or idiopathic angioedema;
- pregnancy or pregnancy planning period, breastfeeding (see section "Use during pregnancy or breastfeeding");
- concomitant use of the drug Pramilet® with aliskiren-containing medicinal products is contraindicated in patients with diabetes mellitus or renal impairment (glomerular filtration rate < 60 ml/min/1.73 m^2) (see section "Interaction with other medicinal products and other forms of interaction");
- concomitant use with sacubitril/valsartan; the drug Pramilet® must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see section "Interaction with other medicinal products and other forms of interaction" and "Administration details").

Associated with amlodipine:
- hypersensitivity to amlodipine or to any other dihydropyridine derivatives;
- severe hypotension;
- shock (in particular cardiogenic shock);
- obstruction of the outflow tract of the left ventricle (high-grade aortic stenosis);
- hemodynamically unstable heart failure after acute myocardial infarction.

Associated with the drug Pramilet®*:*
- all above-mentioned contraindications associated with the use of the individual components are also applicable to the combination medicinal product Pramilet®;
- hypersensitivity to any of the excipients of the drug Pramilet® (see section "Composition").

Interaction with other medicinal products and other forms of interaction.
Interactions associated with lisinopril
Antihypertensive agents
Concomitant use of lisinopril with other antihypertensive agents (e.g. glyceryl trinitrate and other nitrates, or other vasodilators) may result in additive falls in blood pressure.
Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
Dual blockade of the RAAS through the combined use of ACE inhibitors, angiotensin II receptor blockers (ARBs) or aliskiren is associated with a higher risk of hypotension, hyperkalemia and decreased renal function (in particular acute renal failure) compared to the use of monotherapy (see sections "Contraindications", "Administration details").
Medicinal products that may increase the risk of angioedema
Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see sections "Contraindications" and "Administration details").
Concomitant use of ACE inhibitors with mammalian target of rapamycin inhibitors (mTOR) such as temsirolimus, sirolimus, everolimus) or neutral endopeptidase inhibitors (in particular, racecadotril), or tissue plasminogen inhibitors, or vildagliptin may lead to an increased risk of angioedema (see section "Administration details").
Diuretics
When a diuretic is added to the lisinopril therapy, the antihypertensive effect is usually additive. Patients already on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure when lisinopril

is added to the therapy. The risk of symptomatic hypotension with lisinopril can be minimized by discontinuing the diuretic prior to initiation of treatment with lisinopril (see sections "Administration details" and "Dosage and administration").

Potassium supplements or potassium-containing salt substitutes, potassium sparing diuretics and other medicinal products that may increase serum potassium levels

Although serum potassium usually remains within normal limits, hyperkalemia may occur in some patients treated with lisinopril. Potassium sparing diuretics (such as spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium, especially in patients with impaired renal function. Care should also be taken when lisinopril is co-administered with other agents that increase serum potassium, such as trimethoprim and cotrimoxazole (trimethoprim/sulfamethoxazole) as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. Therefore, co-administration of lisinopril with the above-mentioned drugs is not recommended. If concomitant use is indicated, these medicinal products should be used with caution and with periodic monitoring of serum potassium (see section "Administration details").

Ciclosporin

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

Heparin.

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

Diuretic-induced hypokalemia may be reduced in case lisinopril is co-administered with a non-potassium-sparing diuretic.

Lithium preparations

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium preparations with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased lithium toxicity with ACE inhibitors. Concomitant use of lisinopril with lithium preparations is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section "Administration details").

Non-steroidal anti-inflammatory medicinal products (NSAIDs), in particular acetylsalicylic acid ≥ 3 g/day

When ACE-inhibitors are co-administered with NSAIDs (acetylsalicylic acid at anti-inflammatory dosage regimens, cyclooxygenase-2 inhibitors (COX-2) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor renal function. These effects are usually reversible. The combination should be administered with caution, especially in elderly patients. Patients should be adequately hydrated and consideration should be given to monitoring the renal function after the beginning of concomitant therapy, as well as throughout the treatment.

Gold

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

Tricyclic antidepressants/antipsychotics/anesthetics

Concomitant use of certain anesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section "Administration details").

Sympathomimetics
Sympathomimetics may reduce the antihypertensive effect of ACE inhibitors.
Hypoglycemic agents
Concomitant administration of ACE inhibitors and hypoglycemic medicinal products (insulins, oral hypoglycemic agents) may potentiate the hypoglycemic effect with a risk of hypoglycemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.
Medicinal products known to cause bone marrow suppression (immunosuppressive agents, allopurinol, procainamide)
Co-administration with lisinopril may lead to an increased risk of neutropenia and/or agranulocytosis (see section "Administration details").
Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates
Lisinopril may be used concomitantly with acetylsalicylic acid (at cardiologic doses), thrombolytics, beta-blockers and/or nitrates.
Interactions associated with amlodipine
Effects of other medicinal products on amlodipine
CYP3A4 isoenzyme inhibitors
Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides such as erythromycin or clarithromycin, verapamil or diltiazem) may cause a significant increase in amlodipine concentrations resulting in an increased risk of hypotension. The clinical manifestations of these pharmacokinetic variations may be more pronounced in elderly patients. Clinical monitoring and amlodipine dose adjustment may thus be required.
Clarithromycin is a CYP3A4 inhibitor. Patients co-treated with clarithromycin and amlodipine have an increased risk of hypotension. Close medical monitoring of patients is recommended in case of concomitant use of amlodipine with clarithromycin.
CYP3A4 isoenzyme inducers
Upon co-administration with known inducers of the CYP3A4 isoenzyme, the plasma amlodipine concentrations may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 isoenzyme inducers (such as rifampicin, *Hypericum perforatum*).
Administration of amlodipine with grapefruit or grapefruit juice is not recommended as this may increase amlodipine bioavailability in some patients resulting in increased hypotensive effects.
Dantrolene (infusion)
In animal studies, administration of verapamil and intravenous dantrolene was associated with ventricular fibrillation and cardiovascular collapse with associated hyperkalemia and subsequent fatal outcome. Due to the risk of hyperkalemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.
Effects of amlodipine on other medicinal products
The hypotensive effect of amlodipine potentiates the respective effects of other medicinal products with antihypertensive properties.
Tacrolimus
Co-administration of tacrolimus with amlodipine may be associated with increased tacrolimus blood levels; the mechanism of this interaction is not fully understood. In order to avoid toxicity of tacrolimus, monitoring of tacrolimus blood levels throughout amlodipine therapy and, when appropriate, dose adjustment of tacrolimus are required.
Mammalian target of rapamycin inhibitors (mTOR)
mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates.

Amlodipine is a weak CYP3A inhibitor. Concomitant use of amlodipine with mTOR inhibitors, the exposure of the latter may increase.
Ciclosporin
No drug interaction studies have been conducted with ciclosporin and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where increased ciclosporin blood concentrations were observed (by 0–40% average). Consideration should therefore be given to monitoring blood ciclosporin levels in such patients throughout amlodipine therapy, and ciclosporin dose reductions should be made as necessary.
Simvastatin
Co-administration of multiple doses of 10 mg of amlodipine with 80 mg of simvastatin resulted in a 77 % increase in exposure to simvastatin compared to simvastatin monotherapy. The dose of simvastatin in patients on amlodipine should be lowered to 20 mg daily.
In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, or warfarin.

Administration details.
All the following administration details associated with the administration of the individual components, are also associated with the combination medicinal product Pramilet®.
Administration details associated with lisinopril
Symptomatic hypotension
Symptomatic hypotension is rarely seen in patients with uncomplicated hypertension.
Significant hypotension may occur in patients who have been volume-depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, vomiting, as well as in patients with severe renin-dependent hypertension (see sections “Interaction with other medicinal products and other forms of interaction” and “Adverse reactions”).
In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. Such cases are most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatremia or functional renal impairment. In patients at an increased risk of symptomatic hypotension, parameters of the hypotensive effect should be monitored following the administration of the initial dose. Similar considerations apply to patients with ischemic heart disease or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If hypotension occurs, the patient should be placed in the supine position with their lower extremities elevated, and, if necessary, should receive fluid replacement (intravenous infusion of normal saline). Transient hypotension is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.
In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with lisinopril. This effect is anticipated and is not usually a reason to discontinue treatment. If hypotension becomes symptomatic, dose reduction or discontinuation of lisinopril may be necessary.
Hypotension in acute myocardial infarction
Treatment with lisinopril must not be initiated in acute myocardial infarction patients who are at risk of further serious hemodynamic deterioration after treatment with a vasodilator. These are patients with a systolic blood pressure of 100 mm Hg or lower, or those in cardiogenic shock. During the first 3 days following the infarction, the dose should be reduced if the systolic blood pressure is 120 mm Hg or lower. Maintenance doses should be reduced to 5 mg or temporarily to 2.5 mg if systolic blood pressure is 100 mm Hg or lower. If hypotension persists (systolic blood pressure less than 90 mm Hg for more than 1 hour) then lisinopril should be withdrawn.
Aortic and mitral valve stenosis/hypertrophic cardiomyopathy

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

Renal impairment

In cases of renal impairment (creatinine clearance < 80 ml/min), the initial lisinopril dose should be adjusted according to the patient's creatinine clearance, and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine is part of standard medical practice for such patients.

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

In some patients with bilateral renal artery stenosis or with a stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency.

If renovascular hypertension is also present, there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above conditions, they should be discontinued, and renal function should be monitored during the first weeks of lisinopril therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when lisinopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of diuretics and/or lisinopril may be required.

In acute myocardial infarction, treatment with lisinopril should not be initiated in patients with evidence of renal dysfunction, defined as serum creatinine concentrations exceeding 177 µmol/l and/or proteinuria exceeding 500 mg/24 h. If renal dysfunction develops during treatment with lisinopril (serum creatinine concentration exceeding 265 µmol/l or a doubling from the pre-treatment value), the physician should consider withdrawal of lisinopril.

Proteinuria

Rare cases of proteinuria have been reported, in particular in patients with impaired renal function or after high doses of lisinopril. In case of clinically significant proteinuria (greater than 1 g/day), the drug is to be prescribed only after assessing the benefits and potential risks of treatment and under constant control of the patient’s clinical and biochemical parameters.

Hypersensitivity/angioedema

Isolated cases of angioedema of the face, extremities, lips, tongue, glottis and/or larynx have been reported in patients treated with ACE inhibitors, including lisinopril. Angioedema may occur at any time during therapy. In such cases, lisinopril should be discontinued immediately and appropriate treatment and medical monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. Even in cases of tongue swelling not associated with respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

Very rarely, fatalities have been reported due to angioedema associated with laryngeal edema or tongue edema. Patients with involvement of the tongue, glottis or larynx, are likely to experience airway obstruction, especially those with a history of airway surgery. In such cases emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of the patient's airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

ACE inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at an increased risk of angioedema while receiving an ACE inhibitor (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 forms of interaction").
Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (such sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk of angioedema (e.g. swelling 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 starting racecadotril, mTOR inhibitors and vildagliptin in patients already taking ACE inhibitors.
Anaphylactoid reactions in hemodialysis patients
Anaphylactoid reactions have been reported in patients undergoing dialysis with high flux membranes (e.g. AN 69) and treated concomitantly with an ACE inhibitor. In such patients, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.
Anaphylactoid reactions during low-density lipoprotein (LDL) apheresis
In isolated cases, patients receiving ACE inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. Such reactions can be avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.
Desensitization
Patients receiving ACE inhibitors during desensitization treatment (e.g. with *Hymenoptera venom*) have sustained anaphylactoid reactions. In such patients, these reactions have been avoided when ACE inhibitors were temporarily withheld but they have reappeared upon inadvertent re-administration of the medicinal product.
Hepatic failure
Very rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant necrosis and sometimes death. The mechanism of this syndrome is not understood. Patients receiving lisinopril who develop jaundice or marked elevations of hepatic enzymes should discontinue lisinopril and receive appropriate medical follow-up.
Neutropenia/agranulocytosis
Neutropenia/agranulocytosis, thrombocytopenia and anemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Neutropenia and agranulocytosis are reversible after discontinuation of the ACE inhibitor.
Lisinopril should be prescribed with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. Periodic laboratory testing (monitoring of white blood cell counts) is advised during lisinopril therapy and patients should be instructed to report any sign of infection.
Dual blockage of the renin-angiotensin-aldosterone system (RAAS)
Concomitant use of ACE-inhibitors, angiotensin II receptor blockers (ARBs) or aliskiren increases the risk of hypotension, hyperkalemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, ARBs or

aliskiren is therefore not recommended ("Interaction with other medicinal products and other forms of interaction").
If dual RAAS blockade is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.
ACE-inhibitors and ARBs should not be used concomitantly in patients with diabetic nephropathy.
Race
ACE inhibitors cause a higher rate of angioedema in black patients than in patients of other races. As with other ACE inhibitors, lisinopril may be less effective in lowering blood pressure in black patients than in non-black patients, possibly because of a higher prevalence of low renin states in the black hypertensive population.
Cough
Cough has been reported with the use of ACE inhibitors. The cough is usually non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.
Surgery/anesthesia
In patients undergoing major surgery or during 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, it can be corrected by volume expansion.
Hyperkalemia
ACE inhibitors can cause hyperkalemia because they inhibit the release of aldosterone. The effect is usually clinically insignificant in patients with normal renal function. However, in patients with impaired renal function, type 2 diabetes and/or in patients taking potassium supplements (in particular salt substitutes), potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), as well as in patients taking other agents that may raise serum potassium levels (e.g., heparin, trimethoprim or co-trimoxazole combination drug (trimethoprim/sulfamethoxazole)) and especially aldosterone antagonists or angiotensin-receptor blockers, hyperkalemia can occur. Potassium-sparing diuretics and angiotensin-receptor blockers should be used with caution in patients receiving ACE inhibitors. Serum potassium and renal function should be monitored regularly is concomitant use of the above agents is required (see section ("Interaction with other medicinal products and other forms of interaction").
Diabetic patients
In diabetic patients treated with oral hypoglycemic agents or insulin, glycemia 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").
Lithium preparations
The combination of lithium preparations and lisinopril is generally not recommended (see section "Interaction with other medicinal products and other forms of interactions").
Administration details associated with amlodipine
The safety and efficacy of amlodipine in hypertensive crisis has not been established.
Heart failure
Patients with heart failure should use amlodipine with caution. In a long-term, placebo-controlled study in patients with severe heart failure (class III and IV according to the New York Heart Association classification, NYHA) the reported incidence of pulmonary edema was higher in the amlodipine-treated group than in the placebo group.
Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Hepatic impairment
The half-life of amlodipine is prolonged and AUC values raised in patients with hepatic impairment, however, appropriate dosage recommendations have not been established. Amlodipine should therefore be initiated at the lower end of the dosing range. Caution should be exercised both when initiating the treatment and when increasing the dose. Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.
Elderly patients
Care should be exercised when increasing the dosage in elderly patients (see sections "Pharmacokinetics" and "Dosage and administration").
Renal impairment
Amlodipine may be used at normal doses in such patients. Changes in amlodipine plasma concentrations are not correlated with the degree of renal impairment. Amlodipine is not dialysable.
Administration details associated with the drug Pramilet®
This medicinal product contains less than 1 mmol (23 mg) sodium per tablet, therefore, it is essentially sodium-free.

Use during pregnancy or breastfeeding.
Pregnancy
The drug Pramilet® is contraindicated in pregnant women and those planning pregnancy (see section "Contraindications").
No experience is available with the use of lisinopril and amlodipine in pregnant women in adequately controlled clinical studies. However, the use of both active substances is not recommended or is contraindicated (see section "Composition" for information regarding the active substances).
If pregnancy is diagnosed during treatment with the drug Pramilet®, it should be discontinued immediately, or, if necessary, replaced with a drug allowed for use in pregnancy (see section "Administration details").
The drug Pramilet® should not be initiated during pregnancy. If it is absolutely necessary to continue therapy with the drug Pramilet®, patients planning pregnancy should be switched to alternative hypotensive agents with an established safety profile for use in pregnancy.
Lisinopril use
Epidemiological data regarding the risk of teratogenicity associated with the use of ACE inhibitors during the first trimester of pregnancy has not been conclusive, however a small increase of the risk cannot be excluded. Unless continued therapy with an ACE inhibitor is considered essential, patients planning pregnancy should be changed to alternative hypotensive drugs which have an established safety profile for use in pregnancy. If pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.
Exposure to ACE inhibitors during the second and third trimesters is known to induce fetotoxicity (decreased renal function, oligohydramnios, retardation of skull ossification) and neonatal toxicity (renal failure, hypotension, hyperkalemia). Should exposure to ACE inhibitors have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Neonates and infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections "Contraindications" and "Administration details").
Amlodipine use
The safety of amlodipine use in pregnant women has not been established.

In animal studies, reproductive toxicity was observed at high doses. Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and the fetus.

Breastfeeding

There is no information on the use of lisinopril during breastfeeding. Amlodipine is excreted in breast milk. The proportion of the maternal dose of amlodipine received by the infant has been estimated with an interquartile range of 3−7 %, with a maximum of 15 %. The effect of amlodipine on infants has not been estimated.

The drug Pramilet® is contraindicated during breastfeeding, alternative treatments with an established safety profile should be used, particularly when nursing a newborn or preterm infant (see section "Contraindications").

Fertility

No data from adequately controlled clinical studies of the effects of lisinopril and amlodipine on fertility are available.

Amlodipine use

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility.

Effect on reaction rate when driving motor transport or using other mechanisms.

Lisinopril-associated

When driving motor transport or operating other mechanisms it should be taken into account that occasionally dizziness or tiredness may occur.

Amlodipine-associated

Amlodipine can have minor or moderate influence on the ability to drive vehicles and use other mechanisms. Patients suffering from dizziness, headache, fatigue or nausea may have an impaired ability to react. Caution is recommended especially at the start of treatment.

In accordance with the above, the drug Pramilet® may affect the ability to drive motor transport and use other mechanisms (especially at the start of treatment).

Dosage and administration.

Doses

The recommended dose is 1 tablet per day. The maximum daily dose is 1 tablet.

Fixed-dose combinations are usually not appropriate for initial therapy.

The choice of the drug Pramilet® (see table below) depends on the established optimal maintenance doses of lisinopril and amlodipine.

Optimal maintenance doses		The drug Pramilet®
Amlodipine	*Lisinopril*	
5 mg	10 mg	Pramilet®, tablets 5 mg/10 mg
5 mg	20 mg	Pramilet®, tablets 5 mg/20 mg
10 mg	20 mg	Pramilet®, tablets 10 mg/20 mg

Patients with renal impairment

To find the optimal starting dose and maintenance dose for patients with renal impairment, the patients should be individually titrated using the individual components of lisinopril and amlodipine.

Renal function, serum potassium and sodium levels should be monitored during therapy with the drug Pramilet®. In case of deterioration of renal function, the drug Pramilet® should be discontinued and replaced by the adequately adjusted individual components. Amlodipine is not dialysable.

Patients with hepatic impairment
Dosage recommendations have not been established in patients with mild to moderate hepatic impairment, therefore doses should be selected with caution and starting at the lower end of the dosing range (see sections "Pharmacokinetics" and "Administration details"). To find the optimal starting dose and maintenance dose for patients with hepatic impairment, the patients should be individually titrated using the individual components of lisinopril and amlodipine in the form of tablets.
The pharmacokinetics of amlodipine have not been studied in severe hepatic impairment. Amlodipine should be initiated at the lowest dose and titrated slowly in patients with severe hepatic impairment.
Elderly patients (above 65 years of age)
The drug should be used with caution in elderly patients.
In clinical studies, there was no age-related change in the efficacy or safety profile of amlodipine or lisinopril. To find the optimal maintenance dose for elderly patients they should be individually titrated using the individual components of lisinopril and amlodipine in the form of tablets.
Method of administration
For oral administration. Since food intake does not affect the absorption of the medicinal product, the drug Pramilet® may be taken regardless food intake, that is, before, during or after eating.

Children.
The safety and efficacy of using the drug Pramilet® in children (under 18 years of age) have not been established.

Overdose.
No data are available for Pramilet® overdose in humans.
Lisinopril overdose
Limited data are available for overdose in humans. Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, increased heart rate, bradycardia, dizziness, anxiety and cough. The recommended treatment of overdose is intravenous infusion of saline solution. If hypotension occurs, the patient should be placed horizontally on his back. The treatment with angiotensin II infusion and/or intravenous catecholamines infusion 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 "Administration details"). If therapy-resistant bradycardia occurs, pacemaker therapy is indicated. Vital signs, blood serum electrolytes and creatinine concentrations should be monitored constantly.
Amlodipine overdose
Data for intentional overdose in humans are limited.
Symptoms
Overdosage could result in excessive peripheral vasodilatation with reflex tachycardia. Marked and prolonged systemic hypotension up to shock with fatal outcome has been reported.
Non-cardiogenic pulmonary edema has rarely been reported to be a consequence of amlodipine overdose, which may manifest with delayed onset (24–48 hours post-ingestion) and require ventilatory support. The precipitating factors for non-cardiogenic pulmonary edema development may be early resuscitative measures (including fluid overload) for maintaining perfusion and cardiac output.

Treatment
Clinically significant hypotension due to amlodipine overdosage calls for active measures for cardiovascular support including frequent monitoring of cardiac and respiratory systems function, the patient should be placed in the supine position with their lower extremities elevated (above the head level) and circulating blood volume and urine output should be controlled.
Vasopressors may be needed for restoring vascular tone and blood pressure provided that there is no contradiction to their use. Intravenous calcium gluconate infusion may be beneficial in reversing the effects caused by calcium channel blockade.
In some cases, gastric lavage may be worthwhile. In the studies involving healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine.
Since amlodipine is highly protein-bound, dialysis is of no benefit.
Overdose with the drug Pramilet® may lead to excessive peripheral vasodilatation with marked hypotension and acute vascular insufficiency, electrolyte disturbances, renal failure, hyperventilation, tachycardia, increased heart rate, bradycardia, dizziness, anxiety and cough. Symptomatic treatment (placing the patient in the supine position, monitoring and, if necessary, support of the cardiac and respiratory function, controlling blood pressure, circulating blood volume and electrolyte balance as well as serum creatinine concentrations) is recommended. In case of marked hypotension, the patient should be placed on his back, the lower extremities should be elevated above the head. If the administration of fluid does not elicit sufficient response, supportive treatment with administration of peripheral vasopressors may be necessary, unless contradicted. Treatment with angiotensin II infusion may also be considered. Intravenous administration of calcium gluconate may be beneficial in reversing the effects caused by calcium channel blockade.
Lisinopril can be removed from the systemic circulation by hemodialysis. The use of high flux polyacrylonitrile membranes during dialysis is not recommended.

Adverse reactions.
The frequency category is defined as follows: very common (≥ 1/10); common (from ≥ 1/100 to < 1/10); uncommon (from ≥ 1/1 000 to < 1/100); rare (from ≥ 1/10 000 to < 1/1 000); very rare (< 1/10000); frequency unknown (cannot be estimated from the available data).
Within each frequency group the adverse reactions are represented in the descending order of seriousness.
Adverse reactions observed and registered during treatment with lisinopril and amlodipine separately:
Lisinopril
Blood and lymphatic system disorders: rare – decreased hemoglobin, decreased hematocrit; very rare – bone marrow depression, anemia, agranulocytosis (see section "Administration details"), leucopenia, neutropenia, thrombocytopenia, hemolytic anemia, lymphadenopathy.
Immune system disorders: rare – autoimmune disorders; frequency unknown – anaphylactic/anaphylactoid reaction.
Endocrine disorders: rare – syndrome of inappropriate antidiuretic hormone secretion (SIADH).
Metabolic and nutrition disorders: very rare – hypoglycemia.
Psychiatric disorders: uncommon – mood alterations, sleep disturbances, hallucinations; rare – confusion; frequency unknown – depression.
Nervous system disorders: common – dizziness, headache; uncommon – vertigo, paresthesia, dysgeusia; rare – smell disturbances; frequency unknown – syncope.
Heart disorders: uncommon – myocardial infarction, possibly secondary to excessive hypotension in high-risk patients (see section "Administration details"), tachycardia, palpitations.

Vascular system disorders: common – orthostatic effects (including orthostatic hypotension); uncommon – cerebrovascular accident (stroke), possibly secondary to excessive hypotension in high-risk patients (see section "Administration details"), tachycardia, Raynaud's syndrome.
Respiratory, thoracic and mediastinal disorders: common – cough; uncommon – rhinitis; very rare – bronchospasm, allergic alveolitis/eosinophilic pneumonia, sinusitis.
Gastro-intestinal disorders: common – diarrhea, vomiting; uncommon – abdominal pain, nausea, dyspepsia; rare – dry mouth; very rare – pancreatitis, intestinal angioedema.
Hepatobiliary disorders: rare – liver failure, hepatitis – hepatocellular or cholestatic, jaundice (see section "Administration details").
Skin and subcutaneous tissue disorders: uncommon – rash, pruritus; rare – psoriasis, urticaria, alopecia, hypersensitivity / angioedema of the face, extremities, lips, tongue, glottis and/or larynx (see section "Administration details"); rare – toxic epidermal necrolysis, Stevens – Johnson syndrome, erythema multiforme, pemphigus, sweating, benign lymphadenosis of the skin*.
Renal and urinary disorders: common – renal dysfunction; rare – acute renal failure, uremia; very rare – oliguria/anuria.
Reproductive system and breast disorders: uncommon – impotency; rare – gynecomastia.
General disorders and administration site conditions: uncommon – fatigue, asthenia.
Laboratory investigations: uncommon – serum urea and creatinine concentrations increased, hyperkalemia, hepatic enzymes increased; very rare – serum bilirubin increased, hyponatremia.
Amlodipine.
Blood and lymphatic system disorders: very rare – thrombocytopenia, leucopenia.
Immune system disorders: very rare – allergic reactions.
Metabolic and nutrition disorders: very rare – hyperglycemia.
Psychiatric disorders: uncommon – insomnia, mood alterations (including anxiety), depression; rare – confusion.
Nervous system disorders: common – sleepiness, dizziness, headache (especially at the beginning of treatment); uncommon – syncope, tremor, dysgeusia, hypesthesia, paresthesia; rare – hypertonia, peripheral neuropathy; frequency unknown – extrapyramidal disorders.
Eye disorders: common – vision impairment (including diplopia).
Ear and labyrinth disorders: uncommon – tinnitus.
Heart disorders: common – palpitations; uncommon – arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation); very rare – myocardial infarction.
Vascular system disorders: common – skin hyperemia; uncommon –hypotension; very rare – vasculitis.
Respiratory, thoracic and mediastinal disorders: common – dyspnea; uncommon – cough, rhinitis.
Gastro-intestinal disorders: common – abdominal pain, nausea, dyspepsia, defecation disorders (diarrhea and constipation); uncommon – vomiting, dry mouth; very rare – pancreatitis, gastritis, gingival hyperplasia.
Hepatobiliary disorders: very rare – hepatitis, jaundice, hepatic enzymes increased **.
Skin and subcutaneous tissue disorders: uncommon – alopecia, purpura, skin discoloration, hyperhidrosis, pruritus, skin rash, exanthema, urticaria; very rare – Quincke's edema, exfoliative dermatitis, Stevens – Johnson syndrome, erythema multiforme, angioedema, photosensitivity; frequency unknown – toxic epidermal necrolysis.
Musculo-skeletal system and connective tissue disorders: common – ankle swelling (ankle joint), muscle cramps; uncommon – arthralgia, myalgia, back pain.
Renal and urinary disorders: uncommon – urination disorder, nocturia, increased urinary frequency.
Reproductive system and breast disorders: uncommon – impotence, gynecomastia.

General disorders and administration site conditions: very common – edemas; common – fatigue, asthenia; uncommon – chest pain, pain, malaise.
Laboratory investigations: uncommon – increase in body weight, decrease in body weight.
*A symptom complex has been reported, which may include one or several of the following symptoms: fever, vasculitis, myalgia, arthralgia/arthritis, positive antinuclear antibodies (ANA), elevated erythrocyte sedimentation rate (ESR), eosinophilia and leucocytosis, rash, photosensitivity or other dermatological manifestations.
**Most frequently associated with cholestasis.
Safety data of clinical studies suggest that lisinopril is usually well tolerated by hypertensive children and adolescents, and that the safety profile in this age group is comparable to that in adults.
Reporting of suspected adverse reactions
Reporting suspected 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 at a temperature not more than 25 °C.
Keep out of reach of children.

Package.
10 tablets are in a blister. 3 or 9 blisters are in a carton package.

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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