APPROVED
The Order of Ministry of Health of Ukraine
16.06.2021 № 1225
Registration certificate
№ UA/18781/01/01
№ UA/18781/01/02

INSTRUCTION
for medical use

BARATON®

Composition:
active substance: ramipril;
each tablet contains 5 mg or 10 mg ramipril;
excipients: low-substituted hydroxypropylcellulose, mannitol (E 421), calcium carbonate, sodium stearyl fumarate, iron oxide yellow (E 172).

Pharmaceutical form. Tablets.
Basic physical and chemical properties:
5 mg tablets: yellow or light yellow tablets with a distinctive yellow pigment, round, flat, with a breakline on one side and smooth on the other side;
10 mg tablets: yellow or light yellow tablets with a distinctive yellow pigment, oval, biconvex, smooth on both sides.

Pharmacotherapeutic group. Angiotensin-converting enzyme inhibitors (ACE). ACE inhibitors alone. Ramipril. ATC code C09A A05.

Pharmacological properties.
Pharmacodynamics.
Mechanism of action
Ramiprilat, the active metabolite of the prodrug ramipril, inhibits the enzyme dipeptidylcarboxypeptidase I (synonyms: ACE; kininase II). In plasma and tissues this enzyme catalyses the conversion of angiotensin I to the active vasoconstrictor substance (vasoconstrictor) angiotensin II, as well as the breakdown of the active vasodilator bradykinin. Reduced angiotensin II formation and inhibition of bradykinin breakdown lead to vasodilatation.
Since angiotensin II also stimulates the release of aldosterone, ramiprilat causes a reduction in aldosterone secretion. The average response to ACE inhibitor monotherapy was lower in black (Afro-Caribbean) hypertensive patients (usually a low-renin hypertensive population) than in non-black patients.
Pharmacodynamics.
Antihypertensive properties
Administration of ramipril causes a marked reduction in peripheral arterial resistance. Generally, there are no major changes in renal plasma flow or glomerular filtration rate (GFR). Administration of ramipril to patients with hypertension leads to a reduction in supine and standing blood pressure without a compensatory rise in heart rate.

In most patients the onset of the antihypertensive effect of a single dose becomes apparent 1 to 2 hours after administration. The peak effect of a single dose is usually reached in 3 to 6 hours. The antihypertensive effect of a single dose usually lasts for 24 hours.
The maximum antihypertensive effect of continued treatment with ramipril is generally apparent after 3 to 4 weeks. It has been shown that, under long term therapy, the antihypertensive effect is sustained for 2 years.
Abrupt discontinuation of ramipril does not produce a rapid and excessive increase in blood pressure (rebound effect).
Heart failure. In addition to conventional therapy with diuretics and optional cardiac glycosides, ramipril has been shown to be effective in patients with functional classes II-IV of the NYHA. The drug has beneficial effects on cardiac hemodynamics (decreased left and right ventricular filling pressures, reduced total peripheral vascular resistance, increased cardiac output and improved cardiac index). It also reduces neuroendocrine activation.
Clinical efficacy and safety
Cardiovascular prevention/Nephroprotection
A preventive placebo-controlled study (the HOPE-study) was carried out in more than 9,200 patients who received ramipril in addition to standard therapy. Patients with increased risk of cardiovascular disease following either atherothrombotic cardiovascular disease (history of coronary heart disease, stroke or peripheral vascular disease) or diabetes mellitus with at least one additional risk factor (documented microalbuminuria, hypertension, elevated total cholesterol level, low-density lipoprotein cholesterol level or cigarette smoking) were included in the study.
The study showed that ramipril statistically significantly decreases the incidence of myocardial infarction, cardiovascular death and stroke, alone and combined (primary combined endpoint).

The HOPE study: Main results

Indicator	Ramipril %	Placebo %	relative risk (95% confidence interval (CI))	p-value
All patients	n=4,645	n=4,652		
Primary combined endpoint	*14*	*17,8*	*0,78 (0,7−0,86)*	*<0,001*
Myocardial infarction	*9,9*	*12,3*	*0,80 (0,7−0,9)*	*<0,001*
Cardiovascular death	*6,1*	*8,1*	*0,74 (0,64−0,87)*	*<0,001*
Stroke	*3,4*	*4,9*	*0,68 (0,56−0,84)*	*<0,001*
Secondary endpoints				
Death from any cause	*10,4*	*12,2*	*0,84 (0,75−0,95)*	*0,005*
Need for Revascularisation	*16,0*	*18,3*	*0,85 (0,77−0,94)*	*0,002*
Hospitalisation for unstable angina	*12,1*	*12,3*	*0,98 (0,87−1,1)*	*NS*
Hospitalisation for heart failure	*3,2*	*3,5*	*0,88 (0,7−1,1)*	*0,25*
Complications related to diabetes	*6,4*	*7,6*	*0,84 (0,72−0,98)*	*0,03*

The MICRO-HOPE study, a predefined substudy from HOPE, investigated the effect of the addition of ramipril 10 mg to the current medical regimen versus placebo in 3577 patients over 55 years of age (with no upper limit of age) with a majority of type 2 diabetes (and at least another CV risk factor), normotensive or hypertensive.
The primary analysis showed that 117 (6,5 %) participants on ramipril and 149 (8,4 %) on placebo developed overt nephropathy, which corresponds to a relative risk reduction 24 %; 95 % CI [3-40], p = 0,027.

The REIN study, a multicenter randomized, double-blind parallel group, placebo-controlled study aimed at assessing the effect of treatment with ramipril on the rate of decline of glomerular filtration rate (GFR) in 352 normotensive or hypertensive patients (18-70 years old) suffering from mild (i.e. mean urinary protein excretion > 1 and < 3 g per day) or severe proteinuria (i.e. mean urinary protein excretion ≥ 3 g per day) due to chronic non-diabetic nephropathy. Both subpopulations were prospectively stratified.
Results of the main analysis of patients with the most severe proteinuria (stratum prematurely disrupted due to benefit in ramipril group) showed that the mean rate of GFR decline per month was lower with ramipril than with placebo; -0,54 (0,66) vs. -0,88 (1,03) ml/min/month, p = 0,038. The intergroup difference was thus 0,34 [0,03-0,65] ml/min/month and around 4 ml/min/year; 23,1 % of the patients in the ramipril group reached the combined secondary endpoint of doubling of serum creatinine concentration and/or end-stage renal disease (need for hemodialysis or renal transplantation) - vs. 45,5 % in the placebo group (p = 0,02).
Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
Two large randomised, controlled trials [ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)] have examined the use of combination of an ACE-inhibitor with an angiotensin II receptor blocker.
ONTARGET study was conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.
These studies have shown no significant beneficial effect of combined therapy on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given the similar pharmacodynamic properties of these drugs, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.
ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.
ALTITUDE (Aliskiren Trial in patients with Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Death due to cardiovascular disease and stroke as well as serious adverse events of interest (hyperkalemia, hypotension and renal dysfunction) were reported more frequently in the aliskiren group compared to the placebo group.
Secondary prevention after acute myocardial infarction
The AIRE study included more than 2000 patients with transient/persistent clinical signs of heart failure after documented myocardial infarction. The ramipril treatment was started 3 to 10 days after acute myocardial infarction. The study showed that after an average follow-up time of 15 months the mortality in ramipril-treated patients was 16,9 % and in the placebo treated patients was 22,6 %. This means an absolute mortality reduction of 5,7 % and a relative risk reduction of 27 % (95 % CI [11-40 %]).
Pediatric Population
In a randomized, double-blind placebo-controlled clinical study involving 244 patients with hypertension (73% primary hypertension), aged 6-16 years, patients received either low doses, medium doses or high doses of ramipril to achieve plasma concentrations of ramiprilat, corresponding to the adult dose range of 1,25 mg; 5 mg and 20 mg on the basis of body weight. At the end of 4 weeks, ramipril was ineffective in the endpoint of lowering systolic blood pressure but lowered diastolic blood pressure at the highest dose in the range under study. Both medium and high doses of ramipril showed significant reduction of both systolic and diastolic blood pressure in children with confirmed hypertension.

This effect was not seen in a 4 week randomized, double-blind, dose-escalation withdrawal study in 218 pediatric patients aged 6-16 years (75% primary hypertension). During this study after the drug withdrawal both diastolic and systolic blood pressures demonstrated a modest rebound increase but it was not statistically significant for pressure to return to the baseline, in all groups of tested ramipril dose ranges [low dose (0,625 – 2,5 mg), medium dose (2,5 – 10 mg) or high dose (5 – 20 mg)] based on body weight. Ramipril did not have a linear dose response in the pediatric population studied.

Pharmacokinetics.

Absorption

Following oral administration ramipril is rapidly absorbed from the gastrointestinal tract. Peak plasma concentrations are reached within one hour. Based on urinary recovery, the extent of absorption is at least 56 % and is not significantly influenced by the presence of food in the gastrointestinal tract. The bioavailability of the active metabolite ramiprilat after oral administration of 2,5 mg and 5 mg ramipril is 45 %.

Peak plasma concentrations of ramiprilat, the sole active metabolite of ramipril are reached 2-4 hours after ramipril intake. Steady state plasma concentrations of ramiprilat after once daily dosing of ramipril with the usual doses of ramipril are reached by about the fourth day of treatment.

Distribution

The serum protein binding of ramipril is about 73 % and that of ramiprilat about 56 %.

Metabolism

Ramipril is almost completely metabolised to ramiprilat, the diketopiperazine ester, the diketopiperazine acid and the glucuronides of ramipril and ramiprilat.

Elimination

Excretion of the metabolites is primarily renal. Plasma concentrations of ramiprilat decline in a polyphasic manner. Because of its potent, saturable binding to ACE and slow dissociation from the enzyme, ramiprilat shows a prolonged terminal elimination phase at very low plasma concentrations.

After multiple once-daily doses of ramipril, the effective half-life was 13-17 hours for the 5-10 mg doses and longer for the lower 1,25-2,5 mg doses. This difference is related to the saturable capacity of the enzyme to bind ramiprilat.

Patients with renal impairment (see section “Dosage and administration”)

Renal excretion of ramiprilat is reduced in patients with impaired renal function, and renal ramiprilat clearance is proportionally related to creatinine clearance. This results in elevated plasma concentrations of ramiprilat, which decrease more slowly than in subjects with normal renal function.

Patients with hepatic impairment (see section “Dosage and administration”).

In patients with impaired liver function, the metabolism of ramipril to ramiprilat was delayed due to diminished activity of hepatic esterases and plasma ramipril levels in these patients were increased. Peak concentrations of ramiprilat in these patients, however, are not different from those seen in subjects with normal hepatic function.

Breastfeeding

After a single oral dose of ramipril, its level in breast milk was below the limit of detection. However the effect of multiple doses is not known.

Pediatric Population

The pharmacokinetic profile of ramipril was studied in 30 pediatric hypertensive patients, aged 2-16 years, weighing >10 kg. After doses of 0,05 to 0,2 mg/kg, ramipril was rapidly and extensively metabolized to ramiprilat. Peak plasma concentrations of ramiprilat occurred within 2-3 hours. Ramiprilat clearance highly correlated with body weight ($p<0,01$) as well as the drug dose ($p<0,001$). Clearance and volume of distribution increased with increasing children age for each dose group. The dose of 0,05 mg/kg in children achieved exposure levels comparable to those in adults treated with ramipril 5 mg. The dose of 0,2 mg/kg in children resulted in exposure levels higher than when using the maximum recommended dose of 10 mg per day in adults.

Preclinical safety data

Oral administration of ramipril has been found to be devoid of acute toxicity in animals (rodents and dogs). Studies involving chronic oral administration have been conducted in rats, dogs and monkeys. Indications of electrolyte shifts and changes in the blood cell count have been found in all these three species. As an expression of the pharmacodynamic activity of ramipril, pronounced enlargement of the juxtaglomerular apparatus has been noted in dogs and monkeys receiving the drug at a dose of 250 mg/kg per day. Rats, dogs and monkeys tolerated daily doses of the drug of 2; 2,5 and 8 mg/kg per day of the body weight respectively. Notably, they did not experience adverse effects.

Reproduction toxicology studies in rats, rabbits and monkeys did not disclose any teratogenic properties of the drug. No adverse effects on fertility were observed in male or female rats.
The administration of ramipril to female rats during pragnancy and lactation produced irreversible renal damage (dilatation of the renal pelvis) in the offspring at daily doses of 50 mg/kg body weight or higher.
Extensive mutagenicity testing using several test systems has yielded no indication that ramipril possesses mutagenic or genotoxic properties.

Clinical particulars.

Indications.

- Treatment of hypertension.
- Cardiovascular prevention: reduction of cardiovascular morbidity and mortality in patients with:
  - manifest atherothrombotic cardiovascular disease (history of coronary heart disease or stroke, or peripheral vascular disease);
  - diabetes mellitus with at least one cardiovascular risk factor (see section «Pharmacological properties»).
- Treatment of renal disease:
  - incipient glomerular diabetic nephropathy as defined by the presence of microalbuminuria;
  - manifest glomerular diabetic nephropathy as defined by macroproteinuria in patients with at least one cardiovascular risk factor (see section «Pharmacological properties»);
  - manifest glomerular non-diabetic nephropathy as defined by macroproteinuria ≥ 3 g/day (see section «Pharmacological properties»).
- Treatment of symptomatic heart failure.
- Secondary prevention after acute myocardial infarction: reduction of mortality from the acute phase of myocardial infarction in patients with clinical signs of heart failure when started > 48 hours following acute myocardial infarction.

Contraindications.

- Hypersensitivity to the active substance or to any of the excipients of the drug or any other ACE inhibitors.
- History of angioedema (hereditary, idiopathic or due to previous angioedema with ACE inhibitors or Angiotensin II receptor blockers).
- Concomitant use with sacubitril/valsartan (see also sections “Interaction with other medicinal products and other forms of interaction” and “Administration details”).
- Concomitant use of extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section “Interaction with other medicinal products and other forms of interaction”).
- Significant bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney.
- Pregnancy and pregnancy planning (see section “Use during pregnancy or breastfeeding”).
- Ramipril should not be used in patients with hypotensive or hemodynamically unstable states.
- The concomitant use of ramipril with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1,73 м^2) (see sections

"Pharmacodynamics" and "Interaction with other medicinal products and other forms of interaction").

Interaction with other medicinal products and other forms of interaction.
Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalemia and renal impairment (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections "Pharmacodynamics", "Contraindications" and "Administration details").
Contraindicated combinations
Sacubitril/valsartan
Concomitant use of ACE inhibitors with *sacubitril/valsartan* is contraindicated due to the increased risk of angioedema (see sections "Contraindications" and "Administration details"). Treatment with ramipril should only be initiated after 36 hours following the last dose of sacubitril/valsartan. Treatment with sacubitril/valsartan should only be initiated after 36 hours following the last dose of ramipril.
Extracorporeal therapy
Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or hemofiltration with certain high-flux membranes (e.g. polyacrylonitril membranes) and low-density lipoprotein apheresis with dextran sulphate due to increased risk of severe anaphylactoid reactions (see section "Contraindications"). If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agents.
Combinations requiring precautions
Potassium salts, heparin, potassium sparing diuretics and other active substances, increasing a potassium level in blood plasma (including angiotensin II blockers, trimethoprim and its fixed combinations with sulfamethoxazole, tacrolimus, cyclosporine).
Hyperkalemia may occur, therefore monitoring of serum potassium is recommended.
Antihypertensive agents (e.g. diuretics) and other substances that may decrease blood pressure (e.g. nitrates, tricyclic antidepressants, anesthetics, alcohol, baclofen, alfuzosin, doxazosin, prazosin, tamsulosin, terazosin).
Potentiation of the risk of hypotension is to be anticipated (see section "Administration details" regarding diuretics).
Vasopressor sympathomimetics and other substances (e.g. isoproterenol, dobutamine, dopamine, epinephrine) that may reduce the antihypertensive effect of ramipril
Blood pressure monitoring is recommended.
Allopurinol, immunosuppressants, corticosteroids, procainamide, cytostatics and other substances that may affect the blood cell count
Increased likelihood of hematological reactions (see section "Administration details").
Lithium salts
Excretion of lithium may be reduced by ACE inhibitors and therefore lithium toxicity may be increased. Lithium level should be monitored.
Antidiabetic agents including insulin. Hypoglycemic reactions may occur. Blood glucose monitoring is recommended.
Non-steroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid
Reduction of the antihypertensive effect of ramipril is to be anticipated. Furthermore, concomitant use of ACE inhibitors with NSAIDs may lead to an increased risk of worsening of renal function and to an increase of blood potassium levels.
Salt. Excessive salt intake may reduce the hypotensive effect of the drug.
Specific hyposensitization. ACE inhibition leads to an increased likelihood and severity of anaphylactic and anaphylactoid reactions to insect venom. This effect is believed to be observed in relation to other allergens as well.

mTOR inhibitors or DDP-4 inhibitors
Concomitant use of such medicinal products as mTOR inhibitors (for example, temsirolimus, everolimus, sirolimus) or vildagliptin may lead to an increased risk of angioedema. Caution should be exercised when initiating such treatment (see section "Administration details").
Neprilysin inhibitors (NEP)
There have been reports about a possibility of an increased risk of angioedema in case of concomitant use of ACE inhibitors and NEP inhibitors such as racecadotril (see section "Administration details").
Sacubitril/valsartan
Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema.

Administration details.
Special patient groups
Pregnancy
Treatment with ACE inhibitors or angiotensin II receptor blockers should not be initiated during pregnancy. If continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to an alternative anti-hypertensive drug with an established safety profile for use in pregnancy. If pregnancy is diagnosed, treatment with ACE inhibitors/angiotensin II receptor blockers should be stopped immediately and, if necessary, alternative therapy should be initiated (see section "Contraindications" and "Use during pregnancy or breastfeeding").
Patients with a particular risk of hypotension
- *Patients with significantly increased RAAS activity*

The risk of an acute pronounced fall in arterial blood pressure and deterioration of renal function due to ACE inhibition is increased in patients with strongly activated RAAS, especially if an ACE inhibitor or a concomitant diuretic is given for the first time or at first dose increase.
Significant increase of RAAS activity that requires medical supervision, including continuous monitoring of arterial blood pressure, is to be anticipated, for example, in patients:
- with severe hypertension;
- with decompensated congestive heart failure;
- with hemodynamically relevant left ventricular inflow or outflow impediment (e.g. with stenosis of the aortic or mitral valve);
- with unilateral renal artery stenosis with a second functional kidney;
- who have or may develop fluid or electrolyte depletion (including those receiving diuretics);
- with liver cirrhosis and/or ascites;
- undergoing major surgery or during anesthesia with agents that cause hypotension.

Generally, it is recommended to correct dehydration, hypovolemia or electrolyte depletion before initiating treatment (in patients with heart failure, however, such corrective actions must be carefully evaluated in terms of the risk of volume overload).
- *Dual RAAS blockade*

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalemia and decreased renal function (including acute renal failure). Dual RAAS blockade through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections "Pharmacodynamics" and "Interaction with other medicinal products and other forms of interaction").
If such dual blockade therapy is considered absolutely necessary, it should only be used under specialist supervision and be subject to frequent close monitoring of renal function, electrolytes and arterial blood pressure.
ACE inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

- *Transient or persistent heart failure after myocardial infarction.*
- *Patients at risk of cardiac or cerebral ischemia in case of acute hypotension.*

Special medical supervision is required during the initial phase of treatment.

- *Elderly patients*
  See section "Dosage and administration".

Surgery

It is recommended that treatment with ACE inhibitors such as ramipril is discontinued one day before surgery, if possible.

Monitoring of renal function

Renal function should be assessed before and during treatment and dosage adjusted, especially in the first weeks of treatment. Particularly careful monitoring is required in case of renal impairment (see section "Dosage and administration"). There is a risk of renal function impairment, particularly in patients with congestive heart failure or after renal transplantation, as well as in case of renal vascular lesions, including in patients with hemodynamically relevant unilateral renal artery stenosis.

Angioedema

Individual cases of angioedema in patients who received ACE inhibitors, including ramipril, have been reported (see section "Adverse reactions"). Concomitant use of such medicinal products as mammalian target of rapamycin inhibitors (mTOR) (e.g. temsirolimus, everolimus, sirolimus), vildagliptin or NEP inhibitors (such as racecadotril) may lead to an increased risk of angioedema (the signs include swelling of the airways or tongue, with or without respiratory impairment).

Combination of ramipril with sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see sections "Contraindications" and "Interaction with other medicinal products and other forms of interaction").

In case of angioedema, the drug should be discontinued and emergency therapy initiated. Patients should be kept under medical supervision for at least 12-24 hours until complete resolution of the symptoms.

Intestinal angioedema has been reported in patients treated with ACE inhibitors (see section "Adverse reactions"). These patients complained of abdominal pain (with or without nausea/vomiting).

Anaphylactic reactions during desensitization

The likelihood and severity of anaphylactic and anaphylactoid reactions to insect venom and other allergens are increased during the administration of ACE inhibitors. Temporary discontinuation of ramipril should be considered prior to desensitization.

Electrolyte monitoring. Hyperkalemia

Hyperkalemia has been observed in some patients receiving ACE inhibitors including ramipril. The risk of hyperkalemia is higher in patients with impaired renal function, those over 70 years of age, those with uncontrolled diabetes mellitus, in those receiving potassium salts, potassium-sparing diuretics and other active substances that increase potassium levels, or patients with conditions such as dehydration, acute cardiac decompensation, metabolic acidosis. If concomitant administration of the above-mentioned drugs is considered necessary, regular monitoring of plasma potassium levels is recommended (see section "Interaction with other medicinal products and other forms of interaction").

Electrolyte monitoring. Hyponatremia

Syndrome of inappropriate antidiuretic hormone secretion and subsequent hyponatremia has been observed in some patients treated with ramipril. It is recommended that serum sodium levels be monitored regularly in the elderly and in other patients at risk of hyponatremia.

Neutropenia/agranulocytosis

Cases of neutropenia/agranulocytosis, as well as thrombocytopenia and anemia, have been rare. Bone marrow suppression has also been reported. It is recommended to monitor white blood cell count to detect possible leukopenia. More frequent monitoring is recommended at the beginning of treatment and in patients with impaired renal function, those with concomitant collagen disease

(for example, systemic lupus erythematosus or scleroderma) or those receiving other medicinal products that can cause changes in the blood cell count (see sections “Interaction with other medicinal products and other forms of interaction” and “Adverse reactions”).
Ethnic differences
ACE inhibitors cause a higher rate of angioedema in black patients than in white patients. As with other ACE inhibitors, ramipril may be less effective in lowering arterial blood pressure in black patients. This may be due to a higher prevalence of low renin hypertension in the black hypertensive population.
Cough
Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.
Excipients.
This medicinal product contains less than 1 mmol (23 mg)/dose of sodium, therefore is practically sodium-free.

Use during pregnancy or breastfeeding.
Pregnancy
The use of the drug is contraindicated in pregnant women or women planning a pregnancy. If pregnancy is diagnosed during therapy, the drug should be discontinued immediately and, if necessary, another medicinal product approved for use in pregnancy should be initiated (see section “Contraindications”).
Breastfeeding
Because insufficient information is available regarding the use of ramipril during breastfeeding (see section “Pharmacological properties”), it is not recommended to prescribe it for breastfeeding women. Alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing newborns or preterm infants.

Effect on reaction rate when driving motor transport or using other mechanisms.
Some adverse reactions (e.g. symptoms of lowered arterial blood pressure such as dizziness) may impair the patient's ability to concentrate and react and, therefore, constitute a risk in situations where these abilities are of particular importance (e.g. when driving motor transport or using other mechanisms).
This may usually happen at the start of treatment or when changing over from other drugs to ramipril. Following the first dose or subsequent dose expansion it is not advisable to drive motor transport or use other mechanisms for several hours.
Dosage and administration.
The drug is for oral use.
It is recommended to take ramipril each day at the same time. The drug can be taken with or without food because food intake does not influence the bioavailability of the drug (see section “Pharmacological properties”). 5 mg tablets can be split in half to obtain a 2,5 mg dose. They must not be chewed or crushed. If a 1,25 mg dose is prescribed, ramipril preparations with the possibility of such dosage should be considered.
Adults
Diuretic-treated patients
Hypotension may occur following the initiation of therapy with the drug and is more likely in patients treated concurrently with diuretics. Caution is recommended in such cases since these patients may have volume and/or electrolyte depletion.
If possible, the diuretic should be discontinued 2-3 days before the initiation of ramipril therapy (see section “Administration details”). In hypertensive patients in whom the diuretic cannot be discontinued, therapy should be initiated with a 1,25 mg dose. Renal function and blood potassium

levels should be closely monitored. The subsequent dose of ramipril should be adjusted according to the target arterial blood pressure.

Hypertension

The dose should be chosen individually depending on the patient's state (see section "Administration details") and control measurements of arterial blood pressure. Ramipril may be used as monotherapy or in combination with other classes of antihypertensive medicinal products (see sections "Pharmacodynamics", "Contraindications", "Interaction with other medicinal products and other forms of interaction" and "Administration details").

Starting dose

The drug should be started gradually with a recommended starting dose of 2,5 mg per day.

Patients with strongly activated RAAS may experience a significant drop in arterial blood pressure following the starting dose. A starting dose of 1,25 mg is recommended for such patients and their treatment should be initiated under medical supervision (see section "Administration details").

Dose titration and maintenance dose

The dose can be doubled every 2-4 weeks until the target arterial blood pressure is achieved; the maximum dose of ramipril is 10 mg per day. The drug is usually administered once daily.

Prevention of cardiovascular disease

Starting dose

The recommended starting dose of the drug is 2,5 mg once daily.

Dose titration and maintenance dose

Depending on individual tolerability of the drug, the dose should be gradually increased. It is recommended to double the dose after 1-2 weeks of treatment and, after 2-3 weeks, increase it up to the target maintenance dose of 10 mg once daily.

Treatment of renal disease

Patients with diabetes mellitus and microalbuminuria

Starting dose

The recommended starting dose of the drug is 1,25 mg once daily.

Dose titration and maintenance dose

Depending on individual tolerability of the drug, the dose may be subsequently increased. Following 2 weeks of treatment, it is recommended to double the once daily dose to 2,5 mg, and, after another 2 weeks, to 5 mg.

Patients with diabetes mellitus and at least one cardiovascular risk factor

Starting dose

The recommended starting dose of the drug is 2,5 mg once daily.

Dose titration and maintenance dose

Depending on individual tolerability of the drug, the dose should be subsequently increased. The daily dose should be doubled to 5 mg after 1-2 weeks, and to 10 mg after another 2-3 weeks of treatment. The target daily dose is 10 mg.

Patients with non-diabetic nephropathy as defined by macroproteinuria ≥ 3 g per day

Starting dose

The recommended starting dose of the drug is 1,25 mg once daily.

Dose titration and maintenance dose

Depending on individual tolerability of the drug, the dose should be subsequently increased. It is recommended to double the once daily dose to 2,5 mg after 2 weeks of treatment, and to 5 mg after another 2 weeks of treatment.

Symptomatic heart failure

Starting dose

In patients stabilized after diuretic therapy, the recommended starting dose is 1,25 mg daily.

Dose titration and maintenance dose

The dose of ramipril is titrated by doubling it every 1-2 weeks up to a maximum daily dose of 10 mg. It is recommended to divide the dose into 2 administrations.

Secondary prevention after acute myocardial infarction with heart failure

Starting dose
48 hours following myocardial infarction, clinically and hemodynamically stable patients should be prescribed a starting dose of 2,5 mg twice daily for three days. If the starting dose of 2,5 mg is not tolerated, a 1,25 mg twice daily dose should be used for 2 days before increasing is to 2,5 mg and 5 mg twice daily. If the dose cannot be increased to 2,5 mg twice daily, the treatment should be discontinued.
Dose titration and maintenance dose
The daily dose should be subsequently increased by doubling it at intervals of 1-3 days up to the target maintenance dose of 5 mg twice daily.
The maintenance dose is divided into 2 administrations where possible.
If the dose cannot be increased to 2,5 mg twice daily, the treatment should be discontinued. The experience of treating patients with severe heart failure (IV FC according to the New York Heart Association (NYHA) classification) immediately after myocardial infarction is still insufficient. Should the decision be made to treat these patients with ramipril, it is recommended to start the therapy with a dose of 1,25 mg once daily and to exercise particular caution in any dose increase.
Special patient groups
Patients with renal impairment
The daily dose in patients with renal impairment depends on creatinine clearance (see section "Pharmacological properties"):
- if creatinine clearance is ≥60 ml/min, it is not necessary to adjust the starting dose (2,5 mg per day), and the maximum daily dose is 10 mg;
- if creatinine clearance is 30-60 ml/min, it is not necessary to adjust the starting dose (2,5 mg per day), and the maximum daily dose is 5 mg;
- if creatinine clearance is 10-30 ml/min, the starting dose is 1,25 mg per day, and the maximum daily dose is 5 mg;
- hypertensive patients undergoing hemodialysis: ramipril is poorly eliminated by hemodialysis; the starting dose is 1,25 mg and the maximum daily dose is 5 mg; the drug should be administered several hours after hemodialysis is performed.

Patients with hepatic impairment (see section "Pharmacological properties").
In patients with hepatic impairment, treatment with ramipril should be initiated under close medical supervision, and the maximum daily dose should be 2,5 mg.
Elderly
The starting dose should be lower, and subsequent dose titration should be carried out gradually due to a greater chance of undesirable effects, especially in very old and frail patients. A reduced starting dose of 1,25 mg ramipril should be therefore prescribed.
Also see the above-mentioned information regarding dosage in patients receiving diuretics.

Children.
It is not recommended to use ramipril in children under 18 years of age due to the lack of data regarding the efficacy and safety of using the drug in such patients.

Overdose.
The symptoms of overdose with ACE inhibitors may include excessive peripheral vasodilatation (with marked hypotension, shock), bradycardia, electrolyte disturbances, renal failure. The patient's state should be closely monitored. Symptomatic and supportive treatment should be prescribed. Suggested measures include primary detoxification (gastric lavage, administration of absorbents) and measures to restore hemodynamic stability, including administration of α_1-adrenergic agonists or angiotensin II (angiotensinamide). Ramiprilat is the active metabolite of ramipril and is poorly removed from the systemic circulation by hemodialysis.

Adverse reactions.

The safety profile of ramipril includes data about persistent cough and reactions due to hypotension. Serious adverse reactions include angioedema, hyperkalemia, hepatic or renal impairment, pancreatitis, severe skin reactions and neutropenia/agranulocytosis.
Adverse reactions are classified by frequency as follows: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10000 and <1/1000), very rare (<1/10000), not known (frequency cannot be estimated from the available data).
In each group the adverse reactions are presented in order of decreasing severity.
Blood and lymphatic system:
uncommon: eosinophilia;
rare: decreased white blood cell count (including neutropenia or agranulocytosis), decreased red blood cell count, decreased hemoglobin, decreased platelet count;
not known: bone marrow failure, pancytopenia, hemolytic anemia.
Immune system:
not known: anaphylactic and anaphylactoid reactions, elevated levels of antinuclear antibodies.
Endocrine system:
not known: syndrome of inappropriate antidiuretic hormone secretion.
Metabolic and nutrition disorders:
common: elevated blood potassium levels;
uncommon: anorexia, decreased appetite;
not known: decreased blood sodium levels.
Psychiatric disorders:
uncommon: low mood, anxiety, nervousness, restlessness, sleep disturbances, including drowsiness;
rare: confusional state;
not known: attention disturbances.
Nervous system:
common: headache, dizziness;
uncommon: vertigo, paresthesia, ageusia, dysgeusia;
rare: tremor, balance disorder;
not known: cerebral ischemia, including ischemic stroke and transient ischemic attack, impaired psychomotor skills, burning sensation, parosmia.
Eye disorders:
uncommon: visual disturbance, including blurred vision;
rare: conjunctivitis.
Ear and labyrinth disorders:
rare: impaired hearing, tinnitus.
Cardiovascular system:
uncommon: myocardial ischemia, including angina pectoris or myocardial infarction; tachycardia, arrhythmia, palpitations, peripheral edema;
Vascular disorders:
common: hypotension, decreased orthostatic blood pressure, syncope;
uncommon: blushing, flushing sensation;
rare: vascular stenosis, hypoperfusion, vasculitis;
not known: Raynaud's syndrome.
Respiratory system:
common: non-productive irritating cough, bronchitis, sinusitis, dyspnea (shortness of breath);
uncommon: bronchospasm, including aggravation of asthma, nasal congestion.
Gastrointestinal tract:
common: gastrointestinal inflammation, digestive disturbances, abdominal discomfort, dyspepsia, diarrhea, nausea, vomiting;

uncommon: pancreatitis (there have been reports of isolated cases of lethal outcomes with the use of ACE inhibitors), elevated pancreatic enzymes, angioedema of the small intestine, upper abdomen pain, including gastritis, constipation, dry mouth;
rare: glossitis;
not known: aphthous stomatitis.
Hepatobiliary disorders:
uncommon: elevated hepatic enzymes and/or conjugated bilirubin;
rare: cholestatic jaundice, hepatocellular damage;
not known: acute hepatic failure, cholestatic or cytolytic hepatitis (in very rare cases fatal).
Skin and subcutaneous tissue:
common: rash, in particular maculo-papular;
uncommon: angioedema, in very exceptional cases – airway obstruction resulting from angioedema with a possible fatal outcome; pruritus, hyperhidrosis; rare: exfoliative dermatitis, urticaria, onycholysis;
very rare: photosensitivity reaction;
not known: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, pemphigus, aggravated psoriasis, dermatitis psoriasiform, pemphigoid or lichenoid exanthema or enanthema, alopecia.
Musculoskeletal system disorders:
common: muscle spasms, myalgia;
uncommon: arthralgia.
Renal and urinary system disorders:
uncommon: renal impairment, including acute renal failure; increased urine output, worsening of pre-existing proteinuria, elevated blood urea and creatinine.
Reproductive system and breasts:
uncommon: transient erectile impotence, decreased libido;
not known: gynecomastia.
General disorders:
common: chest pain, fatigue;
uncommon: pyrexia;
rare: asthenia.
Pediatric population
The safety of using ramipril was studied in 325 children and adolescents aged 2−16 years in the course of 2 clinical trials. According to the results, the nature and severity of adverse reactions in children were similar to those observed in adults, however, the frequency of some of the reactions was higher in children than in adults, namely: tachycardia, nasal congestion and rhinitis: common in the pediatric population and uncommon in the adult population.
Conjunctivitis: common in the pediatric population and rare in the adult population.
Tremor and urticaria: uncommon in the pediatric population and rare in the adult population.
The overall safety profile for ramipril in pediatric patients does not differ significantly from that in the adults.
Reporting of suspected adverse reactions.
Reporting suspected adverse reactions after the registration of the medicinal product is of great importance. It allows to continue monitoring the correlation of the benefits and risks related to the use of this medicinal product. Healthcare professionals must report all suspected adverse reactions to the State Enterprise "State Expert Center of the Ministry of Health of Ukraine" and to the applicant through the feedback form at the website: https://kusum.ua/pharmacovigilance/.

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.
14 tablets are in a blister. 2 or 6 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.

or

Manufacturer.
LLC “GLADPHARM LLC”.

Address of manufacturer and manufacturing site.
40020, Ukraine, Sumy region, Sumy, Davydovskoho Hryhoriia Str., 54.

Date of last revision. 03.06.2025