INSTRUCTION
for medical use

BARATON®

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

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

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

Pharmacological properties.
Pharmacodynamics.
Mechanism of action
Ramiprilat, the active metabolite of ramipril, inhibits the enzyme dipeptidylcarboxypeptidase I (synonyms: angiotensin-converting enzyme; kininase II). In plasma and tissue this enzyme catalyses the conversion of angiotensin I to the active vasoconstrictor substance 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.
Pharmacodynamic effects.
Antihypertensive properties
Administration of ramipril causes a marked reduction in peripheral arterial resistance. Generally, there are no major changes in renal plasma flow and glomerular filtration rate. 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 antihypertensive effect of a single dose becomes apparent 1 to 2 hours after oral 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 the antihypertensive effect is sustained under long term therapy lasting 2 years.
Abrupt discontinuation of ramipril does not produce a rapid and excessive rebound increase in blood pressure (rebound effect).
Heart failure. Ramipril has been shown to be effective as an adjunct to traditional diuretic therapy and, if necessary, cardiac glycosides in patients with functional classes II–IV of the NYHA. The drug had beneficial effects on cardiac haemodynamics (decreased left and right ventricular filling pressures, reduced total peripheral vascular resistance, increased cardiac output and improved cardiac index). It also reduced neuroendocrine activation.

Clinical efficacy and safety

Cardiovascular prevention/nephroprotection

A preventive placebo-controlled study (the HOPE-study), was carried out in which ramipril was added to standard therapy in more than 9,200 patients. 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 high-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, death from cardiovascular causes and stroke, alone and combined (primary combined events).

The HOPE study: main results

Parameter	Ramipril %	Placebo %	Relative risk (95% confidence interval (CI))	p-value
All patients	n=4.645	n=4.652		
Primary combined events	*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*
Death from cardiovascular causes	*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)*	*inaccurate*
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 3,577 patients at least ≥ 55 years old (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 RRR 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 function 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/24 h) or severe proteinuria (≥ 3 g/24 h) due to chronic non-diabetic nephropathy. Both subpopulations were prospectively stratified.

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] per month, and around 4 ml/min/year; 23.1 % of the patients in the ramipril group reached the combined secondary endpoint of doubling of baseline serum creatinine concentration and/or end-stage renal disease (ESRD) (need for dialysis 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), 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 was a study 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 on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, 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 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. CV death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.
Secondary prevention after acute myocardial infarction
The AIRE study included more than 2,000 patients with transient/persistent clinical signs of heart failure after documented myocardial infarction. The ramipril treatment was started 3 to 10 days after the 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%]).
Paediatric Population
In a randomized, double-blind clinical study involving 244 paediatric patients with hypertension (73% primary hypertension), aged 6-16 years, patients received either low dose, medium dose or high dose 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. Both medium and high doses of ramipril showed significant reduction of both systolic and diastolic BP in children with confirmed hypertension.
This effect was not seen in a 4 weeks dose-escalation, randomized, double-blind withdrawal study in 218 paediatric patients aged 6–16 years (75% primary hypertension), where both diastolic and systolic blood pressures demonstrated a modest rebound but not a statistically significant return to the baseline, in all three dose levels tested low dose (0.625–2.5 mg), medium dose (2.5–10 mg) or high dose (5–20 mg) ramipril based on weight. Ramipril did not have a linear dose response in the paediatric population studied.
Pharmacokinetic properties.
Absorption
Following oral administration ramipril is rapidly absorbed from the gastrointestinal tract: peak plasma concentrations of ramipril 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 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%.
Biotransformation
Ramipril is almost completely metabolised to ramiprilat, and to 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 of ramiprilat concentrations 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 "Administration details")
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 "Administration details")
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.
Lactation
A single oral dose of ramipril produced an undetectable level of ramipril and its metabolite in breast milk. However the effect of multiple doses is not known.
Paediatric population
The pharmacokinetic profile of ramipril was studied in 30 paediatric 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 the log of body weight ($p<0.01$) as well as 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 5mg. The dose of 0.2 mg/kg in children resulted in exposure levels higher than 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). Oral administration of ramipril has been found to be devoid of acute toxicity in rodents and dogs. Studies involving chronic oral administration have been conducted in rats, dogs and monkeys. Indications of plasma electrolyte shifts and changes in blood picture have been found in the 3 species. As an expression of the pharmacodynamic activity of ramipril, pronounced enlargement of the juxtaglomerular apparatus has been noted in the dog and monkey from daily doses of 250 mg/kg/d. Rats, dogs and monkeys tolerated daily doses of 2, 2.5 and 8 mg/kg/d respectively without harmful effects.
Reproduction toxicology studies in the rat, rabbit and monkey did not disclose any teratogenic properties. Fertility was not impaired either in male or in female rats. The administration of ramipril to female rats during the fetal period 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 characteristics.

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) or
  - Diabetes 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 nondiabetic 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 or any other ACE inhibitors.
- History of angioedema (hereditary, idiopathic or due to previous angioedema with ACE inhibitors or angiotensin II receptor antagonists).
- Concomitant use with sacubitril/valsartan (see sections "Interaction with other medicinal products and other forms of interaction" and "Special precautions for use").
- Concomitant use of extracorporeal treatments that lead to blood contact 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 breast-feeding").
- Ramipril should not be used in patients with hypotension or haemodynamically unstable conditions.
- Co-administration of ramipril with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) (see "Pharmacodynamics" and "Interaction with other medicinal products and others forms of interactions").

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, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections "Pharmacodynamics", "Contraindications" and " Special warnings and precautions for use").

<u>Contra-indicated combinations</u>

Sacubitril/valsartan

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to an increased risk of angioneurotic oedema (see sections "Contraindications" and "Special warnings and precautions for use"). Ramipril should only be started 36 hours after the last dose of sacubitril/valsartan. Sacubitril/valsartan treatment should only be started 36 hours after the last dose of ramipril.

Extracorporeal treatment

Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration 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 agent.

Combinations requiring precautions

Potassium salts, heparin, potassium-sparing diuretics and other active substances that increase plasma potassium levels (including angiotensin II antagonists, trimethoprim and its fixed combinations with sulfamethoxazole, tacrolimus, cyclosporine)

Hyperkalaemia may occur, so plasma potassium levels should be closely monitored.

Antihypertensive drugs (e.g. diuretics) and other substances that can lower blood pressure (e.g. nitrates, tricyclic antidepressants, anesthetics, alcohol, baclofen, alfuzosin, doxazosin, prazosin, tamsulosin, terazosin)

An increased risk of hypotension is to be expected (see section "Special warnings and precautions for use" for 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 change the blood cell count

Increased likelihood of haematological reactions (see section "Special warnings and precautions for use").

Lithium salts

Excretion of lithium may be reduced by ACE inhibitors and therefore lithium toxicity may be increased. Lithium level must be monitored.

Antidiabetic agents including insulin. Hypoglycaemic reactions may occur. Blood glucose monitoring is recommended.

Non-steroidal anti-inflammatory drugs and acetylsalicylic acid

Reduction of the antihypertensive effect of Ramipril is to be anticipated. Furthermore, concomitant treatment of ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function and to an increase in kalaemia.

Salt. Excessive salt intake may weaken the hypotensive effect of the drug.

Specific hyposensitization. Due to ACE inhibition, the probability and severity of anaphylactic and anaphylactoid reactions to insect venom increase. It is believed that this effect can also be observed for other allergens.

mTOR inhibitors or DPP-4 inhibitors

Patients receiving concomitant medications such as mTOR inhibitors (e.g. temsirolimus, everolimus, sirolimus) or vildagliptin may be at increased risk of developing angioneurotic edema. Such therapy should be initiated with caution (see section "Special warnings and precautions for use").

Neprilisin inhibitors (NEPs)

A potential increase in the risk of angioneurotic edema has been reported with the concomitant use of ACE inhibitors and NEP inhibitors such as racecadotril (see section "Special warnings and precautions for use").

Sacubitril/valsartan

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to an increased risk of angioneurotic edema.

Special warnings and precautions for use.

Special populations

Pregnancy

ACE inhibitors such as ramipril, or Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued ACE inhibitor/ AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors/ AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections "Contraindications" and "Use during pregnancy and lactation").

Patients at particular risk of hypotension

- *Patients with strongly activated renin-angiotensin-aldosterone system*

Patients with strongly activated renin-angiotensin-aldosterone system are at risk of an acute pronounced fall in blood pressure and deterioration of renal function due to ACE inhibition, especially when an ACE inhibitor or a concomitant diuretic is given for the first time or at first dose increase.

Significant activation of renin-angiotensin-aldosterone system is to be anticipated and medical supervision including blood pressure monitoring is necessary, for example in patients:

- with severe hypertension;
- with decompensated congestive heart failure;
- with haemodynamically relevant left ventricular inflow or outflow impediment (e.g. stenosis of the aortic or mitral valve);
- with unilateral renal artery stenosis with a second functional kidney;
- in whom fluid or salt depletion exists or may develop (including patients with diuretics);
- with liver cirrhosis and/or ascites;
- undergoing major surgery or during anaesthesia with agents that produce hypotension.

Generally, it is recommended to correct dehydration, hypovolaemia or salt depletion before initiating treatment (in patients with heart failure, however, such corrective action must be carefully weighed out against the risk of volume overload).

- *Dual blockade of the renin-angiotensin-aldosterone system (RAAS)*

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

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

- *Transient or persistent heart failure post MI*
- *Patients at risk of cardiac or cerebral ischemia in case of acute hypotension*.

The initial phase of treatment requires special medical supervision.

- *Older people*

See section "Administration details".

Surgery

It is recommended that treatment with angiotensin converting enzyme inhibitors such as ramipril should be discontinued where possible one day before surgery.

Monitoring of renal function

Renal function should be assessed before and during treatment and dosage adjusted especially in the initial weeks of treatment. Particularly careful monitoring is required in patients with renal impairment (see section "Administration details"). There is a risk of impairment of renal function, particularly in patients with congestive heart failure or after a renal transplant, including in patients with hemodynamically significant unilateral renal artery stenosis.

Angioedema

Angioedema has been reported in patients treated with ACE inhibitors including ramipril (see section "Adverse reactions"). The risk of angioedema (signs may include swelling of the airways or tongue with or without respiratory distress) may be increased in patients receiving concomitant medications such as mammalian rapamycin target inhibitors (mTORs) (e.g. temsirolimus, everolimus, sirolimus), vildagliptin or NEP inhibitors (such as racecadotril).

The combination of ramipril with sacubitrile/valsartan is contraindicated due to an increased risk of angioneurotic edema (see sections "Contraindications" and "Interaction with other medicinal products and other forms of interaction").

In case of angioneurotic edema, the drug should be discontinued and immediate therapy prescribed. Patients should be monitored by a physician for at least 12–24 hours until complete resolution of symptoms.

Cases of angioneurotic edema have been reported 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 under ACE inhibition. A temporary discontinuation of Ramipril should be considered prior to desensitization.

Control of electrolyte balance. Hyperkalemia

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

Electrolyte monitoring: hyponatraemia

Syndrome of Inappropriate Antidiuretic Hormone (SIADH) and subsequent hyponatraemia 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 hyponatraemia.

Neutropenia/agranulocytosis

Neutropenia/agranulocytosis, as well as thrombocytopenia and anaemia, have been rarely seen. Bone marrow depression has also been reported. It is recommended to monitor the white blood cell count to permit detection of a possible leucopoenia. More frequent monitoring is advised in the initial phase of treatment and in patients with impaired renal function, those with concomitant collagen disease (e.g. lupus erythematosus or scleroderma), and all those treated with other medicinal products that can cause changes in the blood picture (see sections "Interaction with other medicinal products and other forms of interaction" and "Adverse reactions").

Ethnic differences

ACE inhibitors cause higher rate of angioedema in black patients than in non black patients. As with other ACE inhibitors, ramipril may be less effective in lowering blood pressure in black people than in non black patients, possibly because of a higher prevalence of hypertension with low renin level in the black hypertensive population.

Cough

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Excipients.

This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially sodium-free.

Use during pregnancy and lactation.

Pregnancy.
The drug is contraindicated in pregnant women or women planning to become pregnant. If pregnancy is detected during therapy, the drug should be discontinued immediately and, if necessary, replaced with another drug approved for use by pregnant women (see section "Contraindications").
Lactation period
Because insufficient information is available regarding the use of ramipril during breastfeeding (see section "Pharmacological properties"), ramipril is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Ability to effect the speed of reaction when driving a car or operating other mechanisms.
Some adverse effects (e.g. symptoms of a reduction in 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. operating a vehicle or machinery).
This can happen especially at the start of treatment, or when changing over from other preparations. After the first dose or subsequent increases in dose it is not advisable to drive or operate machinery for several hours.

Posology and method of administration.
The drug is administered orally.
Ramipril is recommended to be taken at the same time every day. The drug can be taken regardless of food intake, as food intake does not affect the bioavailability of the drug (see section "Pharmacological properties"). 5 mg tablets are intended to be divided in half to obtain a dose of 2.5 mg. They should not be chewed or crushed. In the case of a dose of 1.25 mg, ramipril should be used with the possibility of such dosing.
Adults
Diuretic-treated patients
Hypotension may occur following the initiation of treatment with the drug, the development of which is more likely in patients treated concurrently with diuretics. Caution is advised in such cases, as these patients may have a decrease in circulating blood volume and/or electrolytes.
It is advisable to discontinue the diuretic 2–3 days before starting ramipril, if possible (see section "Special warnings and precautions for use"). In patients with hypertension in whom the diuretic is not discontinued, treatment should be initiated at a dose of 1.25 mg. Renal function and blood potassium levels should be closely monitored. Further dosing of ramipril should be adjusted depending on the target blood pressure level.
Hypertension
The dose should be individualised according to the patient profile (see section "Special warnings and precautions for use") and blood pressure control. Ramipril may be used in 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 "Special warnings and precautions for use").
Starting dose
Ramipril should be started gradually with an initial recommended dose of 2.5 mg daily.
Patients with a strongly activated renin-angiotensin-aldosterone system may experience an excessive drop in blood pressure following the initial dose. A starting dose of 1.25 mg is recommended in such patients and the initiation of treatment should take place under medical supervision (see section "Special warnings and precautions for use").
Titration and maintenance dose
The dose can be doubled at interval of two to four weeks to progressively achieve target blood pressure; the maximum permitted dose of ramipril is 10 mg daily. Usually the dose is administered once daily.

Cardiovascular prevention

Starting dose

The recommended initial dose is 2.5 mg of the drug once daily.

Titration and maintenance dose

Depending on the 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 then after 2–3 weeks to increase it to the target maintenance dose of 10 mg once daily.

Treatment of kidney disease

Patients with diabetes mellitus and microalbuminuria

Starting dose

The recommended initial dose is 1.25 mg of the drug once daily.

Titration and maintenance dose

Depending on the patient's tolerability to the active substance, the dose is subsequently increased. Doubling the once daily dose to 2.5 mg after two weeks and then to 5 mg after a further two weeks is recommended.

Patients with diabetes mellitus and at least one cardiovascular risk factor

Starting dose

The recommended initial dose is 2.5 mg of the drug once daily.

Titration and maintenance dose

Depending on the individual tolerability of the drug in subsequent treatment, the dose should be increased. After 1–2 weeks of treatment, it is recommended to double the daily dose to 5 mg, and then to 10 mg after 2–3 weeks of treatment. The target daily dose is 10 mg.

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

Starting dose

The recommended initial dose is 2.5 mg of the drug once daily.

Titration and maintenance dose

Depending on the individual tolerability of the drug in subsequent treatment, the dose should be increased. After 2 weeks of treatment, it is recommended to double the single daily dose to 2.5 mg, and then to 5 mg after 2 weeks of treatment.

Heart failure with clinical manifestations

Starting dose

For patients whose condition has stabilized after treatment with diuretics, the recommended starting dose is 1.25 mg per day.

Titration and maintenance dose

The dose of ramipril is titrated by doubling it every 1–2 weeks until the maximum daily dose of 10 mg is reached. It is desirable to divide the dose into 2 doses.

Secondary prevention after acute myocardial infarction and with heart failure

Starting dose

After 48 hours, following myocardial infarction in a clinically and haemodynamically stable patient, the starting dose is 2.5 mg twice daily for three days. If the initial 2.5 mg dose is not tolerated a dose of 1.25 mg twice a day should be given for two days before increasing to 2.5 mg and 5 mg twice a day. If the dose cannot be increased to 2.5 mg twice a day the treatment should be withdrawn.

Titration and maintenance dose

In the future, the daily dose should be increased by doubling it with an interval of 1-3 days to reach the target maintenance dose of 5 mg 2 times a day.

The maintenance dose is divided in 2 administrations per day where possible.

If the dose cannot be increased to 2.5 mg twice a day treatment should be withdrawn. Sufficient experience is still lacking in the treatment of patients with severe (NYHA IV) heart failure immediately after myocardial infarction. Should the decision be taken to treat these patients, it is

recommended that therapy be started at 1.25 mg once daily and that particular caution be exercised in any dose increase.

Special populations

Patients with renal impairment

Daily dose in patients with renal impairment should be based on creatinine clearance (see section "Pharmacological properties"):

- if creatinine clearance is ≥ 60 ml/min, it is not necessary to adjust the initial dose (2.5 mg/day); the maximal daily dose is 10 mg;
- if creatinine clearance is between 30–60 ml/min, it is not necessary to adjust the initial dose (2.5 mg/day); the maximal daily dose is 5 mg;
- if creatinine clearance is between 10–30 ml/min, the initial dose is1.25 mg/day and the maximal daily dose is 5 mg;
- in haemodialysed hypertensive patients: ramipril is slightly dialysable; the initial dose is 1.25 mg/day and the maximal daily dose is 5 mg; the medicinal product should be administered few hours after haemodialysis is performed.

Patients with hepatic impairment (see section "Pharmacological properties").

In patients with hepatic impairment, treatment with ramipril must be initiated only under close medical supervision and the maximum daily dose is 2.5 mg ramipril.

Elderly patients

Initial doses should be lower and subsequent dose titration should be more gradual because of greater chance of undesirable effects especially in very old and frail patients. A reduced initial dose of 1.25 mg ramipril should be considered.

See also the above information on the dosage of the drug for patients taking diuretics.

Children.

Ramipril is not recommended for use in children below 18 years of age, as there are insufficient data on the efficacy and safety of this drug in such patients.

Overdose.

Symptoms associated with overdosage of ACE inhibitors may include excessive peripheral vasodilatation (with marked hypotension, shock), bradycardia, electrolyte disturbances, and renal failure. The patient should be closely monitored. The treatment should be symptomatic and supportive. Suggested measures include primary detoxification (gastric lavage, administration of adsorbents) and measures to restore haemodynamic stability, including, administration of alpha 1 adrenergic agonists or angiotensin II (angiotensinamide) administration. Ramiprilat, the active metabolite of ramipril is poorly removed from the general circulation by haemodialysis.

Adverse reactions.

The safety profile of ramipril includes persistent dry cough and reactions due to hypotension. Serious adverse reactions include angioedema, hyperkalaemia, renal or hepatic impairment, pancreatitis, severe skin reactions and neutropenia/ agranulocytosis.

Adverse reactions frequency is defined using the following convention: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic system disorders:

uncommon: eosinophilia;

rare: white blood cell count decreased (including neutropenia or agranulocytosis) , red blood cell count decreased, haemoglobin decreased, platelet count decreased;

not known: bone marrow failure, pancytopenia, haemolytic anaemia.

Immune system disorders:

unknown: anaphylactic and anaphylactoid reactions, increased levels of antinuclear antibodies.
Endocrine system disorders:
unknown: syndrome of inappropriate antidiuretic hormone secretion.
Metabolism and nutrition disorders:
often: blood potassium increased;
uncommon: anorexia, decreased appetite;
unknown: blood sodium decreased.
Psychiatric disorders:
uncommon: depressed mood, anxiety, nervousness, restlessness, sleep disturbances, including somnolence;
rare: confusional state;
unknown: disturbance in attention.
Nervous system disorders:
often: headache, dizziness;
uncommon: vertigo, paraesthesia, ageusia, dysgeusia;
rare: tremor, imbalance;
unknown: cerebral ischemia, including ischemic stroke and transient ischemic attack, psychomotor skills impaired, burning sensation, parosmia.
Eye disorders:
uncommon: visual disturbance including blurred vision;
rare: conjunctivitis.
Ear and labyrinth disorders:
rare: hearing impaired, tinnitus.
Cardiac disorders:
uncommon: myocardial ischaemia including angina pectoris or myocardial infarction, tachycardia, arrhythmia, palpitations, oedema peripheral;
Vascular disorders:
common: hypotension, orthostatic blood pressure decreased, syncope;
uncommon: redness, flushing;
rare: vascular stenosis, hypoperfusion, vasculitis;
unknown: Raynaud's phenomenon.
Respiratory disorders:
common: non-productive tickling cough, bronchitis, sinusitis, dyspnoea;
uncommon: bronchospas m including asthma aggravated, nasal congestion.
Gastrointestinal disorders:
common: gastrointestinal inflammation, digestive disturbances, abdominal discomfort, dyspepsia, diarrhea, nausea, vomiting;
uncommon: pancreatitis (cases of fatal outcome have been very exceptionally reported with ACE inhibitors), pancreatic enzymes increased, small bowel angioedema, abdominal pain upper including gastritis, constipation, dry mouth;
rare: glossitis;
unknown: aphtous stomatitis.
Hepatobiliary disorders:
uncommon: hepatic enzymes and/or bilirubin conjugated increased;
rare: jaundice cholestatic, hepatocellular damage;
unknown: acute hepatic failure, cholestatic or cytolytic hepatitis (fatal outcome has been very exceptional).
Skin and subcutaneous tissue disorders:
common: rash in particular maculopapular;
uncommon: angioedema; very exceptionally, the airway obstruction resulting from angioedema may have a fatal outcome; pruritus, hyperhidrosis; rare: exfoliative dermatitis, urticaria, onycholysis,;

very rare: photosensitivity reaction;
unknown: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, pemphigus, psoriasis aggravated, dermatitis psoriasiform, pemphigoid or lichenoid exanthema or enanthema, alopecia.
Musculoskeletal and connective tissue disorders:
common: muscle spasms, myalgia;
uncommon: arthralgia.
Renal and urinary disorders:
uncommon: renal impairment including renal failure acute, urine output increased, worsening of a pre-existing proteinuria, blood urea increased, blood creatinine increased.
Reproductive system and breast disorders:
uncommon: transient erectile impotence, libido decreased;
unknown: gynaecomastia.
General disorders:
common*:* chest pain, fatigue;
uncommon: pyrexia;
rare: asthenia.
Paediatric population
The safety of ramipril was monitored in 325 children and adolescents aged 2–16 years in 2 clinical trials. According to the results, the nature and severity of adverse reactions in children were similar to those observed in adults, but the incidence of some reactions in children was higher than in adults, namely: tachycardia, nasal congestion and rhinitis: common in pediatric populations and uncommon in adult patients.
Conjunctivitis: common in the pediatric population and rare in adult patients.
Tremor and urticaria: uncommon in the pediatric population and rare in adult patients.
The overall safety profile of ramipril in children and adults does not differ significantly.
Reports of suspected adverse reactions.
Reporting suspected adverse reactions after drug registration is an important procedure. This allows you to continue to monitor the benefit/risk balance of this medicine. Healthcare professionals must report all suspected adverse reactions to the State Expert Center of the Ministry of Health of Ukraine and the applicant via the feedback form on the website: https://kusum.ua/pharmacovigilance/.
Shelf life.
2 years.

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

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

Condition of supply.
By prescription.

Manufacturer.
KUSUM PHARM LLC.

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