

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ramipril/amlodipine Krka 10mg/5mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 10 mg ramipril and 5 mg amlodipine (as amlodipine besilate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard (capsule)

The body of capsule is white to almost white colour with imprinted gray to black mark 1005. The cap of the capsule is orange brown colour. The content of the capsule is white to almost white powder with possible crystals. Capsule size No. 0.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ramipril/amlodipine Krka is indicated for treatment of hypertension as substitution therapy in patients adequately controlled with the individual products given concurrently at the same dose level as in the combination, but as separate tablets.

4.2 Posology and method of administration

Posology

Recommended daily dose is one capsule of the given strength.
Fixed-dose combination is not suitable for initial therapy.

Before switching to Ramipril/amlodipine Krka patients should be controlled on stable doses of the monocomponents taken at the same time. The dose of Ramipril/amlodipine Krka should be based on the doses of the individual components of the combination at the time of switching.

If the change of the dosage is needed, it should be carried out by individual titration of the free combination's ingredients.

Special populations

Diuretic-treated patients

In diuretic-treated patients caution is recommended, as in these patients fluid and/or salt depletion may occur. Renal function and serum potassium level should be monitored.

Patients with renal impairment

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

Renal function and serum potassium levels should be monitored during therapy with Ramipril/amlodipine Krka. In the case of renal function deterioration, the use of Ramipril/amlodipine Krka should be discontinued and replaced by the individual components adequately adjusted.

Daily dose of ramipril in patients with renal impairment should be based on creatinine clearance (see section 5.2):

- if creatinine clearance is ≥ 60 ml/min, it is not necessary to adjust the initial dose (2.5 mg/day); the maximal daily dose of ramipril 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 of ramipril is 5 mg;
- if creatinine clearance is between 10-30 ml/min, the initial dose is 1.25 mg/day and the maximal daily dose of ramipril 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.

No dosage adjustment of amlodipine is required for patients with renal impairment.

Amlodipine is not dialyzable. Amlodipine should be administered with particular caution to patients undergoing dialysis (see section 4.4).

Patients with hepatic impairment

In case of hepatic impairment elimination of amlodipine may be elongated. Exact dosage recommendations concerning amlodipine have not been established, but the drug should therefore be administered with special caution in these patients (see section 4.4).

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.

Doses of ramipril 2.5 mg are not possible with this medicinal product.

Elderly patients

The usual doses of amlodipine can be administered to elderly people, however, caution is advised when the dose is increased (see section 5.2).

Initial doses of ramipril should be lower and subsequent dose titration should be more gradual because of a greater chance of undesirable effects. Administration of Ramipril/amlodipine Krka is not recommended in very old and frail patients.

Paediatric population

Ramipril/amlodipine Krka is not recommended for use in children and adolescents below the age of 18 years due to the lack of data on safety and efficacy.

Method of administration

Oral route.

The capsules should be taken orally each day once at the same time of the day with or without food. It must not be chewed or crushed. It should not be taken with grapefruit juice.

4.3 Contraindications

In connection with ramipril:

- History of angioedema (hereditary, idiopathic or due to previous angioedema with ACE inhibitors or angiotensin II receptor antagonists)
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section 4.5)
- Significant bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney
- 2nd and 3rd trimester of pregnancy (see sections 4.4 and 4.6)
- Ramipril must not be used in patients with hypotensive or haemodynamically unstable states
- The concomitant use of Ramipril/amlodipine Krka with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m²) (see sections 4.5 and 5.1)
- Concomitant use with sacubitril/valsartan therapy. Ramipril/amlodipine Krka must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see also sections 4.4 and 4.5).

In connection with amlodipine:

- Severe hypotension.

- Shock (including cardiogenic shock).
- Obstruction of the outflow tract of the left ventricle (e.g., high grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction.

In connection with ramipril/amlodipine:

- All contraindications related to each monocomponent, as listed above, should apply also to the fixed combination of ramipril/amlodipine.
- Hypersensitivity to the active substances, other ACE (Angiotensin Converting Enzyme) inhibitors, dihydropyridine derivatives or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

All warnings related to each monocomponent, as listed below, should also apply also to the fixed combination of ramipril/amlodipine.

In connection with ramipril:

Special populations

Pregnancy

ACE inhibitors such as ramipril, or Angiotensin II Receptor Antagonists (AIIAs) should not be initiated during pregnancy. Unless continued ACE inhibitor/ AIIAs 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/ AIIAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

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.
- patients with decompensated congestive heart failure
- patients with haemodynamically relevant left ventricular inflow or outflow impediment (e.g. stenosis of the aortic or mitral valve).
- patients with unilateral renal artery stenosis with a second functional kidney
- patients in whom fluid or salt depletion exists or may develop (including patients with diuretics)
- patients with liver cirrhosis and/or ascites
- patients 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 4.5 and 5.1).

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 myocardial infarction.
- Patients at risk of cardiac or cerebral ischemia in case of acute hypotension

The initial phase of treatment requires special medical supervision.

Elderly

See section 4.2.

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 4.2). There is a risk of impairment of renal function, particularly in patients with congestive heart failure or after a renal transplant.

Angioedema

Angioedema has been reported in patients treated with ACE inhibitors including ramipril (see section 4.8).

In case of angioedema, ramipril must be discontinued.

Emergency therapy should be instituted promptly. Patient should be kept under observation for at least 12 to 24 hours and discharged after complete resolution of the symptoms.

Intestinal angioedema has been reported in patients treated with ACE inhibitors including ramipril (see section 4.8). These patients presented with abdominal pain (with or without nausea or vomiting).

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 ramipril. Treatment with ramipril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5).

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin in a patient already taking an ACE inhibitor.

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.

Electrolyte Monitoring: Hyperkalaemia

Hyperkalaemia has been observed in some patients treated with ACE inhibitors including ramipril. ACE inhibitors can cause hyperkalemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. Patients at risk for development of hyperkalaemia include those with renal insufficiency, age (> 70 years), uncontrolled diabetes mellitus, or those using potassium salts, potassium retaining diuretics and other plasma potassium increasing active substances (e.g. heparin, trimethoprim or co-trimoxazole also known as trimethoprim/sulfamethoxazole and

especially aldosterone antagonists or angiotensin-receptor blockers), or conditions such as dehydration, acute cardiac decompensation, metabolic acidosis. If concomitant use of the above mentioned agents is deemed appropriate, regular monitoring of serum potassium and renal function is recommended (see section 4.5).

Electrolyte Monitoring: Hyponatraemia

Syndrome of Inappropriate Anti-diuretic 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 and bone marrow depression has also been reported. It is recommended to monitor the white blood cell count to permit detection of a possible leucopenia. 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 4.5 and 4.8).

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 non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

In connection with amlodipine:

The safety and efficacy of amlodipine in hypertensive crisis has not been established.

Patients with cardiac failure

Patients with heart failure should be treated with caution. In a long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group (see section 5.1). 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.

Patients with hepatic impairment

The half life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.

Elderly patients

In the elderly increase of the dosage should take place with care (see sections 4.2 and 5.2).

Patients with renal impairment

Amlodipine may be used in such patients at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialysable.

4.5 Interaction with other medicinal products and other forms of interactions

In connection with ramipril:

Contra-indicated combinations

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 4.3). If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent. Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see section 4.3 and 4.4).

Precautions for use

Potassium salts, heparin, potassium-retaining diuretics and other plasma potassium increasing active substances (including Angiotensin II antagonists, tacrolimus, ciclosporin): Hyperkalaemia may occur, therefore close monitoring of serum potassium is required. Care should also be taken when ramipril is co-administered with other agents that increase serum potassium, such as trimethoprim and co-trimoxazole (trimethoprim/sulfamethoxazole) as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. Therefore, the combination of ramipril with the above-mentioned drugs is not recommended.

Ciclosporin

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

Heparin

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

Antihypertensive agents (e.g. diuretics) and other substances that may decrease blood pressure (e.g. nitrates, tricyclic antidepressants, anaesthetics, acute alcohol intake, baclofen, alfuzosin, doxazosin, prazosin, tamsulosin, terazosin): Potentiation of the risk of hypotension is to be anticipated (see section 4.2 for diuretics)

Dual blockade of the renin-angiotensin-aldosterone system (RAAS) with ACE-inhibitors, angiotensin II receptor blockers or aliskiren

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 4.3, 4.4 and 5.1).

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 4.4).

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.

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk for angioedema (see section 4.4).

In connection with amlodipine:

Effects of other medicinal products on amlodipine

CYP3A4 inhibitors: Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

Clarithromycin: Clarithromycin is an inhibitor of CYP3A4. There is an increased risk of hypotension in patients receiving clarithromycin with amlodipine. Close observation of patients is recommended when amlodipine is co administered with clarithromycin.

CYP3A4 inducers: Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, *hypericum perforatum*).

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

Dantrolene (infusion): In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to 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 blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other medicinal products with antihypertensive properties.

Tacrolimus: There is a risk of increased tacrolimus blood levels when co-administered with amlodipine but the pharmacokinetic mechanism of this interaction is not fully understood. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Mechanistic Target of Rapamycin (mTOR) Inhibitors: mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.

Cyclosporine: No drug interaction studies have been conducted with cyclosporine and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable trough concentration increases (average 0% - 40%) of cyclosporine were observed. Consideration should be given for monitoring cyclosporine levels in renal transplant patients on amlodipine, and cyclosporine dose reductions should be made as necessary.

Simvastatin: Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin or warfarin.

4.6 Fertility, pregnancy and lactation

Given the effects of the individual components in this combination product on pregnancy and lactation:

Ramipril/amlodipine Krka is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy.

Ramipril/amlodipine Krka is not recommended during lactation. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with Ramipril/amlodipine Krka should be made taking into account the benefit of breastfeeding to the child and the benefit of amlodipine therapy to the mother.

Pregnancy

In connection with ramipril:

Ramipril/amlodipine Krka is not recommended during the first trimester of pregnancy (see section 4.4) and contraindicated during the second and third trimesters of pregnancy (see section 4.3).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor 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 should be stopped immediately, and, if appropriate, alternative therapy should be started.

ACE inhibitor therapy exposure during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3). Should exposure to ACE inhibitors have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Newborns whose mothers have taken ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalaemia (see also sections 4.3 and 4.4).

In connection with amlodipine:

The safety of amlodipine in human pregnancy has not been established.

In animal studies, reproductive toxicity was observed at high doses (see section 5.3).

Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

Breastfeeding

In connection with ramipril:

Because insufficient information is available regarding the use of ramipril during breastfeeding (see section 5.2), 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.

In connection with amlodipine:

Amlodipine is excreted in human milk. The proportion of the maternal dose 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 is unknown. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with amlodipine should be made taking into account the benefit of breastfeeding to the child and the benefit of amlodipine therapy to the mother.

Fertility

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. In one rat study, adverse effects were found on male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Ramipril/amlodipine Krka can have minor or moderate influence on the ability to drive and use machines. Some adverse effects (e.g. symptoms of a reduction in blood pressure such as dizziness, headache, fatigue) 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. Caution is recommended especially at the start of treatment.

4.8 Undesirable effects

Summary of the safety profile

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

The most commonly reported adverse reactions during treatment with amlodipine are somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema and fatigue.

Tabulated list of adverse reactions

Adverse reactions frequency is defined using the following convention:

Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

The following adverse drug reactions have been reported during the treatment with ramipril and amlodipine independently:

System organ class	Frequency	Ramipril	Amlodipine
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	
	Very rare		Leukocytopenia, thrombocytopenia
	Not known	Bone marrow failure, pancytopenia, haemolytic anaemia	
Immune system disorders	Very rare		Allergic reactions
	Not known	Anaphylactic or anaphylactoid reactions, antinuclear antibody increased	
Endocrine disorders	Not known	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	
Metabolism and nutrition disorders	Common	Blood potassium increased	
	Uncommon	Anorexia, decreased appetite	
	Very rare		Hyperglycaemia
	Not known	Blood sodium	

System organ class	Frequency	Ramipril	Amlodipine
		decreased	
Psychiatric disorders	Uncommon	Depressed mood, anxiety, nervousness, restlessness, sleep disorder including somnolence	Insomnia, mood changes (including anxiety), depression
	Rare	Confusional state	Confusion
	Not known	Disturbance in attention	
Nervous system disorders	Common	Headache, dizziness	Somnolence, dizziness, headache (especially at the beginning of the treatment)
	Uncommon	Vertigo, paraesthesia, ageusia, dysgeusia,	Tremor, dysgeusia, syncope, hypoesthesia, paraesthesia
	Rare	Tremor, balance disorder	
	Very rare		Hypertonia peripheral neuropathy
	Not known	Cerebral ischemia including ischaemic stroke and transient ischaemic attack, psychomotor skills impaired, burning sensation, parosmia,	Extrapyramidal disorder
Eye disorders	Uncommon	Visual disturbance including blurred vision	Visual disturbance (including diplopia)
	Rare	Conjunctivitis	
Ear and labyrinth disorders	Uncommon		Tinnitus
	Rare	Hearing impaired, tinnitus	
Cardiac disorders	Common		Palpitations
	Uncommon	Myocardial ischemia including angina pectoris or myocardial infarction, tachycardia, arrhythmia, palpitations, oedema peripheral	Arrhythmia, (including bradycardia, ventricular tachycardia and atrial fibrillation)
	Very rare		Myocardial infarction

System organ class	Frequency	Ramipril	Amlodipine
Vascular disorders	Common	Hypotension, orthostatic blood pressure decreased, syncope	Flushing
	Uncommon	Flushing	Hypotension
	Rare	Vascular stenosis, hypoperfusion, vasculitis	
	Very rare		Vasculitis
	Not known	Raynaud's phenomenon	
Respiratory, thoracic and mediastinal disorders	Common	Non-productive tickling cough, bronchitis, sinusitis, dyspnoea	Dyspnoea
	Uncommon	Bronchospasm including asthma aggravated, nasal congestion	Cough, rhinitis
Gastrointestinal disorders	Common	Gastrointestinal inflammation, digestive disturbances, abdominal discomfort, dyspepsia, diarrhoea, nausea, vomiting	Abdominal pain, nausea, dyspepsia, altered bowel habits (including diarrhoea and constipation)
	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	Vomiting, dry mouth
	Rare	Glossitis	
	Very rare		Pancreatitis, gastritis, gingival hyperplasia
	Not known	Aphtous stomatitis	
Hepatobiliary	Uncommon	Hepatic	

System organ class	Frequency	Ramipril	Amlodipine
disorders		enzymes and/or bilirubin conjugated increased	
	Rare	Jaundice cholestatic, hepatocellular damage	
	Very rare		Hepatitis, jaundice, hepatic enzymes increased*
	Not known	Acute hepatic failure, cholestatic or cytolytic hepatitis (fatal outcome has been very exceptional)	
Skin and subcutaneous tissue disorders	Common	Rash in particular maculo-papular	
	Uncommon	Angioedema; very exceptionally, the airway obstruction resulting from angioedema may have a fatal outcome; pruritus, hyperhidrosis	Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, exanthema, urticaria
	Rare	Exfoliative dermatitis, urticaria, onycholysis	
	Very rare	Photosensitivity reaction	Angioedema, erythema, multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity
	Not known	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, pemphigus, psoriasis aggravated, dermatitis psoriasiform, pemphigoid or lichenoid exanthema or enanthema, alopecia	Toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	Common	Muscle spasms, myalgia	Ankle swelling, muscle cramps
	Uncommon	Arthralgia	Arthralgia, myalgia, back pain

System organ class	Frequency	Ramipril	Amlodipine
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	Micturition disorder, nocturia, increased urinary frequency
Reproductive system and breast disorders	Uncommon	Transient erectile impotence, libido decreased	Impotence, gynaecomastia
	Not known	Gynaecomastia	
General disorders and administration site conditions	Very common		Oedema
	Common	Chest pain, fatigue	Fatigue, asthenia
	Uncommon	Pyrexia	Chest pain, pain, malaise
	Rare	Asthenia	
Investigations	Uncommon		Weight increase, weight decrease

*most commonly with cholestasis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

There is no information on overdose with ramipril/amlodipine in humans.

In connection with ramipril:

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 and 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.

In connection with amlodipine:

In humans experience with intentional overdose is limited.

Symptoms

Available data suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Treatment

Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output.

A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10mg has been shown to reduce the absorption rate of amlodipine.

Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: agents acting on the renin-angiotensin system, ACE inhibitors and calcium channel blockers, ATC code: C09BB07

Ramipril

Mechanism of action

Ramiprilat, the active metabolite of the prodrug 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 onset of 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 3 to 6 hours after oral administration. 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.

Clinical efficacy and safety

Cardiovascular prevention:

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).

	Ramipril %	Placebo %	relative risk (95% confidence interval)	p-value
All patients	n=4,645	N=4,652		
Primary combined events	14.0	17.8	0.78 (0.70-0.86)	<0.001
Myocardial infarction	9.9	12.3	0.80 (0.70-0.90)	<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 (0.87-1.10)	NS
Hospitalisation for heart failure	3.2	3.5	0.88(0.70-1.10)	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], $p = 0.027$.

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 the 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. Cardiovascular 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.

Amlodipine

Mechanism of action

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

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces total ischaemic burden by the following two actions:

- 1) Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.
- 2) The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24-hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

Use in Patients with Heart Failure

Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.

A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure.

In a follow-up, long term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive of underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total cardiovascular mortality. In this same population amlodipine was associated with increased reports of pulmonary oedema.

Treatment to prevent heart attack trial (ALLHAT)

A randomized double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug therapies: amlodipine 2.5-10 mg/d (calcium channel blocker) or lisinopril 10-40 mg/d (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/d in mild to moderate hypertension.

A total of 33,357 hypertensive patients aged 55 or older were randomized and followed for a mean of 4.9 years. The patients had at least one additional CHD risk factor, including: previous myocardial infarction or stroke (> 6 months prior to enrolment) or documentation of other atherosclerotic CVD (overall 51.5 %), type 2 diabetes (36.1 %), HDL-C < 35 mg/dL (11.6 %), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9 %), current cigarette smoking (21.9 %).

The primary endpoint was a composite of fatal CHD or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.98 95 % CI(0.90-1.07) $p = 0.65$. Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2 % vs 7.7 %, RR 1.38, 95 % CI [1.25-1.52] $p < 0.001$). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy. RR 0.96 95 % CI [0.89-1.02] $p = 0.20$.

5.2 Pharmacokinetic properties

Ramipril

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 %.

Metabolism

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 4.2)

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 4.2)

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

One single 10 mg oral dose of ramipril produced an undetectable level in breast milk. However the effect of multiple doses is not known.

Amlodipine*Absorption, distribution, plasma protein binding*

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. 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/elimination

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

Use in 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 half-life and an increase in AUC of approximately 40-60 %.

Use in the elderly

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.

5.3 Preclinical safety dataRamipril

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 foetal 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. Irreversible kidney damage has been observed in very young rats given a single dose of ramipril.

Amlodipine

Reproductive toxicology:

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility:

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m² basis).

In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis:

Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m² basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

*Based on patient weight of 50 kg

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents

Hypromellose 6cP
Maize starch, pregelatinised
Cellulose, microcrystalline
Magnesium stearate (E470b)

Capsule shell

Titanium dioxide (E171)
Iron oxide, yellow (E172)
Iron oxide, red (E172)
Iron oxide, black (E172)
Gelatin
Black printing ink (shellac (E904), propylene glycol (E1520), potassium hydroxide (E525), black iron oxide (E172))

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Blister (OPA/aluminium/PVC//aluminium foil): 30, 50, 60, 90 and 100 hard capsules, in a box.

Unit-dose blister (OPA/aluminium/PVC//aluminium foil): 30 x 1, 50 x 1, 60 x 1, 90 x 1 and 100 x 1 hard capsule, in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Krka d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

February 2020