Package leaflet: Information for the patient

Ramipril/amlodipine Krka 5 mg/5 mg hard capsules
Ramipril/amlodipine Krka 5 mg/10 mg hard capsules
Ramipril/amlodipine Krka 10 mg/5 mg hard capsules
Ramipril/amlodipine Krka 10 mg/10 mg hard capsules
Ramipril/Amlodipine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ramipril/amlodipine Krka is and what it is used for

Ramipril/amlodipine Krka contains two active substances called ramipril and amlodipine . Ramipril belongs to a group of medicines called ACE inhibitors (Angiotensin Converting Enzyme inhibitors), while amlodipine belongs to a group of medicines called calcium channel blockers

Ramipril works by:
- Decreasing your body's production of substances that could raise your blood pressure
- Making your blood vessels relax and widen
- Making it easier for your heart to pump blood around your body

Amlodipine works by:
- Relaxing and widening blood vessels, so that blood passes through them more easily.

Ramipril/amlodipine Krka can be used to treat high blood pressure (hypertension) in patients who are adequately controlled with the individual products given concurrently at the same doses level as in the combination, but as separate tablets.

2. What you need to know before you take Ramipril/amlodipine Krka

Do not take Ramipril/amlodipine Krka:
- If you are allergic to ramipril or amlodipine (active substances), any other ACE inhibitor medicines or any other calcium antagonists, or any of the other ingredients of this medicine (listed in section 6).

Signs of an allergic reaction may include a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue, itching, or reddening of the skin.

- If you have ever had a serious allergic reaction called “angioedema”. The signs include itching, hives (urticaria), red marks on the hands, feet and throat, swelling of the throat and tongue, swelling around the eyes and lips, difficulty breathing and swallowing
- If you are having dialysis or any other type of blood filtration. Depending on the machine that is used, Ramipril/amlodipine Krka may not be suitable for you
- If you have kidney problems where the blood supply to your kidneys is reduced (renal artery stenosis)
- During the last 6 months of pregnancy (see section below on "Pregnancy and breast-feeding")
- If your blood pressure is abnormally low (hypotension) or unstable. Your doctor will need to make this assessment
- If you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine called aliskiren
- If you have narrowing of the aortic heart valve (aortic stenosis) or cardiogenic shock (a condition where your heart is unable to supply enough blood to the body).
- If you suffer from heart failure after a heart attack.

Do not take Ramipril/amlodipine Krka if any of the above apply to you. If you are not sure, talk to your doctor before taking Ramipril/amlodipine Krka.

Warnings and precautions

Talk to your doctor or pharmacist before taking **Ramipril/amlodipine Krka.** Tell your doctor, if any of the situations listed below is applicable to you:
- If you have heart, liver or kidney problems
- If you have lost a lot of body salts or fluids (through being sick (vomiting), having diarrhoea, sweating more than usual, being on a low salt diet, taking diuretics (water tablets) for a long time or having had dialysis)
- If you are going to have treatment to reduce your allergy to bee or wasp stings (desensitization)
- If you are going to receive an anesthestic. This may be given for an operation or any dental work. You may need to stop your Ramipril/amlodipine Krka treatment one day beforehand; ask your doctor for advice
- If you have high amounts of potassium in your blood (shown in blood test results)
- If you are taking medicines or have conditions which may decrease sodium levels in your blood. Your doctor may carry out regular blood tests, particularly for checking the levels of sodium in your blood especially if you are elderly.
- If you think that you are (or might become) pregnant. Ramipril/amlodipine Krka is not recommended in the first 3 months of pregnancy and may cause serious harm to your baby after 3 months of pregnancy (see section below on “Pregnancy and breast-feeding”).
- If you have a collagen vascular disease such as scleroderma or systemic lupus erythematosus
- If you had severe increase in blood pressure (hypertensive crisis)
- If you are elderly and your dose needs to be increased
- If you are taking any of the following medicines used to treat high blood pressure:
    - an angiotensin II receptor blocker (ARBs) (also known as sartans – for example valsartan, telmisartan, irbesartan), in particular if you have diabetes-related kidney problems
    - aliskiren
- If you are taking any of the following medicines, the risk of angioedema (rapid swelling under the skin in area such as the throat) is increased:
    - sirolimus, everolimus and other medicines belonging to the class of mTOR inhibitors (used to avoid rejection of transplanted organs)
    - vildagliptin

  Your doctor may check your kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in your blood at regular intervals.
  See also information under the heading “Do not take Ramipril/amlodipine Krka”

If you suffer from sudden swelling of the lips and face, tongue and throat, neck, possibly also hands and feet, difficulty to swallow or to breathe, hives or hoarseness ('angioedema'). This could be a sign of a severe allergic reaction. This may occur at any time during the treatment. Persons with black skin may have a higher risk of suffering from this condition. If you develop such symptoms you should let your doctor know immediately.

Children and adolescents
Ramipril/amlodipine Krka is not recommended for use in children and adolescents below 18 years of age because safety and efficacy of Ramipril/amlodipine Krka in children has not yet been established.

Other medicines and Ramipril/amlodipine Krka

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Tell your doctor if you are taking any of the following medicines.
- Medicines used to relieve pain and inflammation (e.g. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as ibuprofen or indomethacin and acetylsalicylic acid)
- Medicines used for the treatment of low blood pressure, shock, cardiac failure, asthma or allergies such as ephedrine, noradrenaline or adrenaline. Your doctor will need to check your blood pressure.
- Medicines for cancer (chemotherapy)
- Medicines to stop the rejection of organs after a transplant such as ciclosporin
- Diuretics (water tablets) such as furosemide
- Medicines which can increase the amount of potassium in your blood such as spironolactone, triamterene, amiloride, potassium salts, heparin (for thinning blood)
- Steroid medicines for inflammation such as prednisolone
- Allopurinol (used to lower the uric acid in your blood)
- Procainamide (for heart rhythm problems)
- Temsirolimus (for cancer)
- Vildagliptin (used for treating type 2 diabetes)
- Medicines for diabetes such as oral, glucose lowering medicines and insulin. Ramipril/amlodipine Krka may lower your blood sugar amounts. Check your blood sugar amounts closely while taking Ramipril/amlodipine Krka
- Lithium (for mental health problems). Ramipril/amlodipine Krka may increase the amount of lithium in your blood. Your lithium amount will need to be closely checked by your doctor
- Ketoconazole, itraconazole (anti-fungal medicines)
- Ritonavir, indinavir, nelfinavir (so called protease inhibitors used to treat HIV)
- Rifampicin, erythromycin, clarithromycin (antibiotics used for infections caused by bacteria)
- Hypericum perforatum (St. John's Wort)
- Verapamil, diltiazem (medicines to treat heart disorders or high blood pressure)
- Dantrolene (infusion for severe body temperature abnormalities).
- Tacrolimus (used to control your body's immune response, enabling your body to accept the transplanted organ)
- Simvastatin (cholesterol lowering medicine)
- Medicines which are most often used to avoid rejection of transplanted organs (sirolimus, everolimus and other medicines belonging to the class of mTOR inhibitors). See section "Warnings and precautions".
- Potassium supplements or salt substitutes containing potassium, diuretics (water tablets, in particular those so called potassium sparing), other drugs which can increase potassium in your body (such as heparin and co-trimoxazole also known as trimethoprim/sulfamethoxazole).

Your doctor may need to change your dose and/or take other precuations:

If you are taking an angiotensin II receptor blocker (ARB) or aliskiren (see also information under the headings “Do not take Ramipril/amlodipine Krka” and “Warnings and precautions”).

If any of the above apply to you (or you are not sure), talk to your doctor before taking Ramipril/amlodipine Krka.

Ramipril/amlodipine Krka with food, drink and alcohol
Ramipril/amlodipine Krka may be taken with or without food.

- Drinking alcohol with Ramipril/amlodipine Krka may make you feel dizzy or light-headed. If you are concerned about how much you can drink while you are taking Ramipril/amlodipine Krka, discuss this with your doctor as medicines used to reduce blood pressure and alcohol can have additive effects.

Grapefruit juice or grapefruit should not be consumed by people who are taking Ramipril/amlodipine Krka. This is because grapefruit and grapefruit juice can lead to an increase in the blood levels of the active ingredient amlodipine, which can cause an unpredictable increase in the blood pressure lowering effect of Ramipril/amlodipine Krka.

Pregnancy and breast-feeding
Pregnancy
You must tell your doctor if you think that you are (or might become) pregnant.
You should not take Ramipril/amlodipine Krka in the first 12 weeks of pregnancy, and you must not take them at all after the 13th week as their use during pregnancy may possibly be harmful to the baby.
If you become pregnant while on Ramipril/amlodipine Krka, tell your doctor immediately. A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy.

Breast-feeding
You should not take Ramipril/amlodipine Krka if you are breastfeeding. Amlodipine has been shown to pass into breast milk in small amounts. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Ramipril/amlodipine Krka may affect your ability to drive or use machines. If the capsules make you feel sick, dizzy or tired, or give you a headache, do not drive or use machines and contact your doctor immediately. This is more likely to happen when you start taking Ramipril/amlodipine Krka or start taking a higher dose..

3. How to take Ramipril/amlodipine Krka

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Take this medicine by mouth at the same time of the day, before or after your meal.
Swallow the whole capsule with liquid.
Do not take Ramipril/amlodipine Krka with grapefruit juice.
Ramipril/amlodipine Krka should be administered once a day.

Elderly
Your doctor will reduce the initial dose and adjust your treatment more slowly.

If you take more Ramipril/amlodipine Krka than you should
Taking too many capsules may cause your blood pressure to become low or even dangerously low. You may feel dizzy, lightheaded, faint or weak. If blood pressure drop is severe enough shock can

occur. Your skin could feel cool and clammy and you could lose consciousness. Tell a doctor or go to the nearest hospital casualty department straight away. Do not drive to the hospital, get somebody else to take you or call for an ambulance. Take the medicine pack with you. This is so the doctor knows what you have taken.

If you forget to take Ramipril/amlodipine Krka
If you forget to take a capsule, leave out that dose completely. Take your next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

If you stop taking Ramipril/amlodipine Krka
Your doctor will advise you how long to take your medicine. Your condition may return if you stop using your medicine before you are advised.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking Ramipril/amlodipine Krka and see a doctor straight away, if you notice any of the following serious side effects – you may need urgent medical treatment:
- Swelling of the face, lips or throat which make it difficult to swallow or breathe, as well as itching and rashes. This could be a sign of a severe allergic reaction to Ramipril/amlodipine Krka.
- Severe skin reactions including rash, ulcers in your mouth, worsening of a pre-existing skin disease, reddening, blistering or detachment of skin, severe itching, blistering, peeling and swelling of the skin, inflammation of mucous membranes (such as Stevens-Johnson syndrome, toxic epidermal necrolysis or erythema multiform).

Tell your doctor immediately if you experience:
- Faster heart rate, uneven or forceful heartbeat (palpitations), chest pain, tightness in your chest or more serious problems including heart attack and stroke
- Shortness of breath, a cough, sudden wheeziness, chest pain or difficulty in breathing. These could be signs of lung problems
- Bruising more easily, bleeding for longer than normal, any sign of bleeding (e.g. bleeding from the gums), purple spots blotching on the skin or getting infections more easily than usual, sore throat and fever, feeling tired, faint, dizzy or having pale skin. These can be signs of blood or bone marrow problems
- Severe stomach pain which may reach through to your back. This could be a sign of pancreatitis (inflammation of the pancreas).
- Fever, chills, tiredness, loss of appetite, stomach pain, feeling sick, yellowing of your skin or eyes (jaundice). These can be signs of liver problems such as hepatitis (inflammation of the liver) or liver damage.
- Swelling of eyelids or the tongue.
- Allergic reactions.

<u>In connection with ramipril:</u>

Common (may affect up to 1 in 10 people)
- Headache or feeling tired
- Feeling dizzy. This is more likely to happen when you start taking Ramipril/amlodipine Krka or start taking a higher dose
- Fainting, hypotension (abnormally low blood pressure), especially when you stand or sit up quickly
- Dry tickly cough, inflammation of your sinuses (sinusitis) or bronchitis, shortness of breath

- Stomach or gut pain, diarrhoea, indigestion, feeling or being sick
- Skin rash with or without raised area
- Chest pain
- Cramps or pain in your muscles
- Blood tests showing more potassium than usual in your blood.

Uncommon (may affect up to 1 in 100 people)
- Balance problems (vertigo)
- Itching and unusual skin sensations such as numbness, tingling, pricking, burning or creeping on your skin (paraesthesia)
- Loss or change in the way things taste
- Sleep problems
- Feeling depressed, anxious, more nervous than usual or restless
- Blocked nose, difficulty breathing or worsening of asthma
- A swelling in your gut called "intestinal angioedema" presenting with symptoms like abdominal pain, vomiting and diarrhoea
- Heartburn, constipation or dry mouth
- Passing more water (urine) than usual over the day
- Sweating more than usual
- Loss or decrease of appetite (anorexia)
- Increased or irregular heartbeats
- Swollen arms and legs. This may be a sign of your body holding onto more water than usual
- Flushing
- Blurred vision
- Pain in your joints
- Fever
- Sexual inability in men, reduced sexual desire in men or women
- An increased number of certain white blood cells (eosinophilia) found during a blood test
- Blood tests showing changes in the way your liver, pancreas or kidneys are working.

Rare (may affect up to 1 in 1,000 people)
- Feeling shaky or confused
- Red and swollen tongue
- Severe flaking or peeling of the skin, itchy, lumpy rash
- Nail problem (e.g. loosening or separation of a nail from its bed)
- Skin rash or bruising
- Blotches on your skin and cold extremities
- Red, itchy, swollen or watery eyes
- Disturbed hearing and ringing in your ears
- Feeling weak
- Blood tests showing a decrease in the number of red blood cells, white blood cells or platelets or in the amount of haemoglobin.

Very rare (may affect up to 1 in 10,000 people)
- Being more sensitive to the sun than usual.

Not known (frequency cannot be estimated from the available data)
- Concentrated urine (dark in colour), feel or are sick, have muscle cramps, confusion and fits which may be due to inappropriate ADH (anti-diuretic hormone) secretion. If you have these symptoms contact your doctor as soon as possible

Other side effects reported:
Tell your doctor if any of the following gets serious or lasts longer than a few days.
- Difficulty concentrating
- Swollen mouth
- Blood tests showing too few blood cells in your blood

- Blood tests showing less sodium than usual in your blood
- Fingers and toes changing colour when you are cold and then tingling or feeling painful when you warm up (Raynaud's phenomenon)
- Breast enlargement in men
- Slowed or impaired reactions
- Burning sensation
- Change in the way things smell
- Hair loss

In connection with amlodipine:

Very common (may affect more than 1 in 10 people)
- Ankle swelling (oedema)

Common (may affect up to 1 in 10 people)
- Headache, dizziness, sleepiness (especially at the beginning of treatment)
- Palpitations (awareness of your heart beat), flushing
- Abdominal pain, feeling sick (nausea)
- Altered bowel habits, diarrhoea, constipation, indigestion
- Tiredness, weakness
- Visual disturbances, double vision
- Muscle cramps

Other side effects that have been reported include the following list. If any of these get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Uncommon (may affect up to 1 in 100 people)
- Mood changes, anxiety, depression, sleeplessness
- Trembling, taste abnormalities, fainting
- Numbness or tingling sensation in your limbs, loss of pain sensation
- Ringing in the ears
- Low blood pressure
- Sneezing/running nose caused by inflammation of the lining of the nose (rhinitis)
- Cough
- Dry mouth, vomiting (being sick)
- Hair loss, increased sweating, itchy skin, red patches on skin, skin discolouration
- Disorder in passing urine, increased need to urinate at night, increased number of times of passing urine
- Inability to obtain an erection, discomfort or enlargement of the breasts in men
- Pain, feeling unwell
- Joint or muscle pain, back pain
- Weight increase or decrease

Rare (may affect up to 1 in 1,000 people)
- Confusion

Very rare (may affect up to 1 in 10,000 people)
- Decreased numbers of white blood cells, decrease in blood platelets which may result in unusual bruising or easy bleeding (red blood cell damage)
- Excess sugar in blood (hyperglycaemia)
- A disorder of the nerves which can cause weakness, tingling or numbness
- Swelling of the gums
- Abdominal bloating (gastritis)
- Abnormal liver function, inflammation of the liver (hepatitis), yellowing of the skin (jaundice), liver enzyme increase which may have an effect on some medical tests
- Increased muscle tension

- Inflammation of blood vessels, often with skin rash
- Sensitivity to light
- Disorders combining rigidity, tremor, and/or movement disorders

Not known (frequency cannot be estimated from the available data)
- Trembling, rigid posture, mask-like face, slow movements and a shuffling, unbalanced walk

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly 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.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ramipril/amlodipine Krka

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the packaging after EXP. The expiry date refers to the last day of that month.

Do not store above 30°C.
Store in the original package in order to protect from light and moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ramipril/amlodipine Krka contains
- The active substances are ramipril and amlodipine (as amlodipine besilate).
  5 mg/5 mg hard capsules: Each hard capsule contains 5 mg ramipril and 5 mg amlodipine (as amlodipine besilate).
  5 mg/10 mg hard capsules: Each hard capsule contains 5 mg ramipril and 10 mg amlodipine (as amlodipine besilate).
  10 mg/5 mg hard capsules: Each hard capsule contains 10 mg ramipril and 5 mg amlodipine (as amlodipine besilate).
  10 mg/10 mg hard capsules: Each hard capsule contains 10 mg ramipril and 10 mg amlodipine (as amlodipine besilate).
- The other ingredients are hypromellose 6cP, pregelatinised maize starch, microcrystalline cellulose, magnesium stearate (E470b) in the capsule contents.
  The other ingredients of 5 mg/5 mg hard capsules and 10 mg/5 mg hard capsules are titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172), black iron oxide (E172), gelatin, black printing ink (shellac (E904), propylene glycol (E1520), potassium hydroxide (E525), black iron oxide (E172)) in the capsule shell.
  The other ingredients of 5 mg/10 mg hard capsules are titanium dioxide (E171), red iron oxide (E172), gelatin, black printing ink (shellac (E904), propylene glycol (E1520), potassium hydroxide (E525), black iron oxide (E172)) in the capsule shell.
  The other ingredients of 10 mg/10 mg hard capsules are titanium dioxide (E171), red iron oxide (E172), gelatin, white printing ink (shellac (E904), propylene glycol (E1520), potassium hydroxide (E525), titanium dioxide (E171)) in the capsule shell.

What Ramipril/amlodipine Krka looks like and contents of the pack

5 mg/5 mg hard capsules (capsules): The body of capsule is orange brown colour with imprinted black mark 0505. 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. 2.
5 mg/10 mg hard capsules (capsules): The body of capsule is white to almost white colour with imprinted gray to black mark 0510. The cap of the capsule is brownish red colour. The content of the capsule is white to almost white powder with possible crystals. Capsule size No. 0.
10 mg/5 mg hard capsules(capsules): 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.
10 mg/10 mg hard capsules (capsules): The body of capsule is brownish red colour with imprinted white mark 1010. The cap of the capsule is brownish red colour. The content of the capsule is white to almost white powder with possible crystals. Capsule size No. 0.

Ramipril/amlodipine Krka is available in boxes containing:
- 30, 50, 60, 90 and 100 hard capsules in blisters,
- 30 x 1, 50 x 1, 60 x 1, 90 x 1 and 100 x 1 hard capsule in unit-dose blisters.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

This medicinal product is authorised in the Member States of the EEA under the following names:

Germany, Estonia, Finland, Croatia, Slovenia	Rameam
Austria	Ramipril/Amlodipin Krka
Belgium	Ramipril/Amlodipine Krka
Ireland	Ramipril/amlodipine Krka
Bulgaria	Рамеам
Czech Republic, Latvia, Poland, Slovakia	Ramladio
Italy	Ramipril e amlodipina krka
Portugal	Ramipril + amlodipina Krka
Romania	Ramipril/amlodipină Krka

This leaflet was last revised in