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Public Assessment Report

Name of the Product:

Roxampex

10 mg/5 mg/4 mg, 10 mg/5 mg/8 mg, 10 mg/10 mg/8 mg, 20 mg/5 mg/4 mg, 20 mg/5 mg/8 mg, 20 mg/10 mg/8 mg film-coated tablets

(rosuvastatin/amlodipine/perindopril tert-butylamine)

Procedure number: HU/H/0598/001-006/DC

Marketing authorisation holder: Krka d.d.

Dat25 May 2020

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Roxampex 10 mg/5 mg/4 mg, 10 mg/5 mg/8 mg, 10 mg/10 mg/8 mg, 20 mg/5 mg/4 mg, 20 mg/5 mg/8 mg, 20 mg/10 mg/8 mg film-coated tablets. The holder of the marketing authorisation is Krka d.d.

The active substances are rosuvastatin, amlodipine and perindopril tert-butylamine.

- Roxampex 10 mg/5 mg/4 mg film-coated tablets: each film-coated tablet contains 10 mg rosuvastatin equivalent to 10.395 mg rosuvastatin calcium, 5 mg amlodipine equivalent to 6.934 amlodipine besylate and 4 mg perindopril tert-butylamine equivalent to 3.338 mg perindopril.
- Roximpex 10 mg/5 mg/8 mg film-coated tablets: each film-coated tablet contains 10 mg rosuvastatin equivalent to 10.395 mg rosuvastatin calcium, 5 mg amlodipine equivalent to 6.934 amlodipine besylate and 8 mg perindopril tert-butylamine equivalent to 6.676 mg perindopril.
- Roximpex 10 mg/10 mg/8 mg film-coated tablets. each film-coated tablet contains 10 mg rosuvastatin equivalent to 10.395 mg rosuvastatin calcium, 10 mg amlodipine equivalent to 13.870 amlodipine besylate and 8 mg perindopril tert-butylamine equivalent to 6.676 mg perindopril.
- Roximpex 20 mg/5 mg/4 mg film-coated tablets: each film-coated tablet contains 20 mg rosuvastatin equivalent to 20.79 mg rosuvastatin calcium, 5 mg amlodipine equivalent to 6.934 amlodipine besylate and 4 mg perindopril tert-butylamine equivalent to 3.338 mg perindopril.
- Roximpex 20 mg/5 mg/8 mg film-coated tablets: each film-coated tablet contains 20 mg rosuvastatin equivalent to 20.79 mg rosuvastatin calcium, 5 mg amlodipine equivalent to 6.934 amlodipine besylate and 8 mg perindopril tert-butylamine equivalent to 6.676 mg perindopril.
- Roximpex 20 mg/10 mg/8 mg film-coated tablets: each film-coated tablet contains 20 mg rosuvastatin equivalent to 20.79 mg rosuvastatin calcium, 10 mg amlodipine equivalent to 13.87 amlodipine besylate and 8 mg perindopril tert-butylamine equivalent to 6.676 mg perindopril.

The other ingredients are:
- tablet core: microcrystalline cellulose (type 200), microcrystalline cellulose (type 112), crospovidone (type A) colloidal anhydrous silica and magnesium stearate;
- film-coating: polyvinyl alcohol, macrogol 3350, titanium dioxide (E171) and talc as well as
  - 10/5/4 mg strength: yellow iron oxide (E172), red iron oxide (E172), black iron oxide (E172),
  - 10/5/8 strength: yellow iron oxide (E172), red iron oxide (E172), black iron oxide (E172),
  - 10/10/8 strength: yellow iron oxide (E172),

- 20/5/4 strength: yellow iron oxide (E172), red iron oxide (E172),
- 20/5/8 strength: yellow iron oxide (E172).

The appearance of the tablets is:

- The 10 mg/5 mg/4 mg film-coated tablets are off-pink, round, slightly biconvex with bevelled edges, engraved with mark PAR1 on one side of the tablet (tablet diameter: approximately 8.5 mm).
- The 10 mg/5 mg/8 mg film-coated tablets are pale pinkish-brown, round, slightly biconvex with bevelled edges, engraved with mark PAR2 on one side of the tablet (tablet diameter: approximately 8.5 mm).
- The 10 mg/10 mg/8 mg film-coated tablets are yellowish brown, round, slightly biconvex with bevelled edges, engraved with mark PAR3 on one side of the tablet (tablet diameter: approximately 11 mm).
- The 20 mg/5 mg/4 mg film-coated tablets are light orange pink, round, slightly biconvex with bevelled edges, engraved with mark PAR4 on one side of the tablet (tablet diameter: approximately 11 mm).
- The 20 mg/5 mg/8 mg film-coated tablets are light yellow, round, slightly biconvex with bevelled edges, engraved with mark PAR5 on one side of the tablet (tablet diameter: approximately 11 mm).
- The 20 mg/10 mg/8 mg film-coated tablets are white, round, slightly biconvex with bevelled edges, engraved with mark PAR6 on one side of the tablet (tablet diameter: approximately 11 mm).

The film-coated tablets are available in packs in blisters.

Roxampex film-coated tablets (further on: Roxamplex) is a combination of three active ingredients. Rosuvastatin belongs to a group of medicines called statins. Perindopril is an ACE (angiotensin converting enzyme) inhibitor. Amlodipine belongs to a group of medicines called calcium antagonists.

Rosuvastatin helps to control high cholesterol level:

- if the patient is at risk from a heart attack or stroke, rosuvastatin is used to treat high cholesterol;
- if changing the diet and doing more exercise were not enough to correct the cholesterol levels. The patient should continue with the cholesterol-lowering diet and exercise while is taking rosuvastatin.

Perindopril and amlodipine help to control high blood pressure (hypertension).

Roxampex is prescribed in adult patients for treatment of high blood pressure (hypertension) and concomitant high cholesterol level. Patients already taking rosuvastatin, perindopril and amlodipine tablets may instead receive one tablet of Roxampex which contains all three ingredients.

What patients need to know before taking Roxampex

Patients must not take Roxampex if they

- are allergic to rosuvastatin, to perindopril or any other ACE inhibitor, to amlodipine or any other calcium antagonists, or any of the other ingredients of Roxampex;
- have experienced symptoms such as wheezing, swelling of the face or tongue, intense itching or severe skin rashes with previous ACE inhibitor treatment or if you or a member of their family have had these symptoms in any other circumstances (a condition called angioedema);
- have diabetes or impaired kidney function and are treated with a blood pressure lowering medicine containing aliskiren;
- have severe low blood pressure (hypotension);
- have narrowing of the aortic heart valve (aortic stenosis) or cardiogenic shock (a condition where the heart is unable to supply enough blood to the body);
- suffer from heart failure after a heart attack;
- have a severe kidney disease;
- have liver disease;
- have repeated or unexplained muscle aches or pains;
- take a drug called ciclosporin (used, for example, after organ transplants);
- are pregnant or breast-feeding. Those who become pregnant while taking Roxampex, stop taking it immediately and consult the doctor;
- are having dialysis or any other type of blood filtration. Depending on the machine that is used, Roxampex may not be suitable for them;
- have kidney problems where the blood supply to the kidneys is reduced (renal artery stenosis);
- have taken or are currently taking sacubitril/valsartan, a medicine used to treat a type of long-term (chronic) heart failure in adults, as the risk of angioedema (rapid swelling under the skin in an area such as the throat) is increased.

Warnings and precautions

Patients must talk to their doctor before taking Roxampex if they

- reacently have heart attack;
- have aortic valve stenosis (narrowing of the main blood vessel leading from the heart) or hypertrophic cardiomyopathy (heart muscle disease) or renal artery stenosis (narrowing of the artery supplying the kidney with blood);
- have heart failure or any other heart problems;
- have kidney problems or if are receiving dialysis;
- have liver problems;
- suffer from a collagen disease (disease of the connective tissue) such as systemic lupus erythematosus or scleroderma;
- have severe respiratory failure;
- have swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing (angioedema), which can occur at any time during treatment. Stop the treatment immediately and directly contact the doctor;
- are on a salt restricted diet or use salt substitutes which contain potassium;
- are taking lithium or potassium-sparing diuretics (spironolactone, triamterene) as their use with Roxampex should be avoided (see “Taking other medicines”);

- are elderly;
- have abnormally increased levels of a hormone called aldosterone in the blood (primary aldosteronism);
- have diabetes;
- are to undergo anaesthesia and/or major surgery,
- are to undergo LDL apheresis (which is removal of cholesterol from the blood by a machine),
- are going to have desensitisation treatment to reduce the effects of an allergy to bee or wasp stings,
- have recently suffered from diarrhoea or vomiting, or are dehydrated,
- have been told by their doctor that they have an intolerance to some sugars,
- have thyroid gland that does not work properly;
- are of Asian origin – that is Japanese, Chinese, Filipino, Vietnamese, Korean and Indian. Their doctor needs to choose the right starting dose of Roxampex to suit them;
- are of black origin since they may have a higher risk of angioedema and this medicine may be less effective in lowering the blood pressure than in non-black patients;
- have had repeated or unexplained muscle aches or pains, a personal or family history of muscle problems, or a previous history of muscle problems when taking other cholesterol-lowering medicines. Patients must tell their doctor immediately if they have unexplained muscle aches or pains especially if feeling unwell or have a fever. Also they must inform their doctor if they have a muscle weakness that is constant;
- taking other medicines called fibrates to lower the cholesterol;
- are taking medicines used to fight the HIV infection e.g. ritonavir with lopinavir and/or atazanavir (see "Taking other medicines");
- regularly drink large amounts of alcohol;
- 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 having diabetes-related kidney problems;
    - aliskiren;
- women should avoid becoming pregnant while taking Roxampex by using suitable contraception;
- are taking or have taken in the last 7 days a medicine called fusidic acid, (a medicine for bacterial infection) orally or by injection. The combination of fusidic acid and rosuvastatin can lead to serious muscle problems (rhabdomyolysis, see "Other medicines").

The doctor may check the patient's kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in the blood at regular intervals.

If the patient is are taking any of the following medicines, the risk of angioedema may be increased:
- racecadotril (used to treat diarrhea);
- sirolimus, everolimus, temsirolimus and other drugs belonging to the class of so-called mTor inhibitors (used to avoid rejection of transplanted organs);
- vildagliptin, a medicine used to treat diabetes.

Angioedema (a severe allergic reaction with swelling of the face, lips, tongue or throat with difficulty in swallowing or breathing) has been reported in patients treated with ACE inhibitors, including Roxampex. This may occur at any time during treatment. Those who develop such symptoms should stop taking Roxampex and see a doctor immediately.

Those who think they are (or might become) pregnant, should consult it with the doctor. Roxampex is not recommended in early pregnancy, and must not be taken if the patient is more than 3 months pregnant as it may cause serious harm to the baby if used at that stage (see "Pregnancy and Breast-feeding").

In a small number of people, statins can affect the liver. This is identified by a simple test which looks for increased levels of liver enzymes in the blood. For this reason, ythe doctor will usually carry out this blood test (liver function test) before and during treatment with Roxampex.

While being on this medicine, the doctor will monitor the patient closely if the patient has diabetes or is at risk of developing diabetes. The patient is likely to be at risk of developing diabetes if having high levels of sugars and fats in the blood, is overweight and has high blood pressure.

Children and adolescents

Roxampex should not be used in children and adolescents.

Other medicines and Roxampex

Those who are taking, have recently taken or might take any other medicines must consult their doctor. Treatment with Roxampex can be affected by other medicines.

Patients should particularly make sure to inform their doctor if tehy are taking any of the following medicines as special care may be required:

- other medicines for treating high blood pressure, including angiotensin II receptor blockers (ARB), aliskiren (see also information under the headings "Do not take Roxampex" and "Warnings and precautions") or diuretics (medicines which increase the amount of urine produced by the kidneys);
- potassium-sparing diuretics (e.g. triamterene, amiloride), potassium supplements (including salt substitutes) and other medicines that can increase the amount of potassium in the blood (e.g. trimethoprim and co-trimoxazole for infections caused by bacteria; ciclosporin or tacrolimus, immunosuppressant medicines used to prevent organ transplant rejection; and heparin, a medicine used to thin blood to prevent clots),
- potassium-sparing drugs used in the treatment of heart failure: eplerenone and spironolactone at doses between 12.5 mg to 50 mg per day,
- lithium for mania or depression,
- non-steroidal anti-inflammatory drugs (e.g. ibuprofen) or high dose salicylates (e.g. aspirin);
- medicines to treat diabetes (such as insulin or metformin),
- baclofen (to treat muscle stiffness occurring in diseases such as multiple sclerosis);

- medicines to treat mental disorders such as depression, anxiety, schizophrenia etc (e.g. tricyclic antidepressants, antipsychotics),
- trimethoprim (for the treatment of infections),
- estramustine (used in cancer therapy),
- medicines, which are most often used to treat diarrhoea (racecadotril) or avoid rejection of transplanted organs (sirolimus, everolimus, temsirolimus and other drugs belonging to the class of so-called mTor inhibitors). See section "Warnings and precautions",
- allopurinol (for the treatment of gout),
- procainamide (for the treatment of an irregular heart beat),
- vasodilators including nitrates (products that make the blood vessels become wider),
- heparin (medicines used to thin blood),
- medicines used for the treatment of low blood pressure, shock or asthma (e.g. ephedrine, noradrenaline or adrenaline),
- gold salts, especially with intravenous administration (used to treat symptoms of rheumatoid arthritis),
- warfarin or clopidogrel (or any other drug used for thinning the blood),
- fibrates (such as gemfibrozil, fenofibrate) or any other medicine used to lower cholesterol (such as ezetimibe),
- indigestion remedies (used to neutralise acid in the stomach),
- rifampicin, erythromycin, clarithromycin (antibiotics),
- an oral contraceptive (the pill) or hormone replacement therapy,
- anti-viral medications such as ritonavir with lopinavir and/or atazanavir or simeprevir (used to treat infections, including HIV or hepatitis C infection – see “Warnings and precautions”),
- hypericum perforatum (St. John’s Wort),
- verapamil, diltiazem (heart medicines),
- dantrolene (infusion for severe body temperature abnormalities),
- simvastatin (cholesterol lowering medicine).

If the patient needs to take oral fusidic acid to treat a bacterial infection, he/she will need to temporarily stop using this medicine. The doctor will tell the patient when it is safe to restart. Taking with fusidic acid may rarely lead to muscle weakness, tenderness or pain (rhabdomyolysis).

The doctor may need to change the dose and/or to take other precautions if the patient ise taking an angiotensin II receptor blocker (ARB) or aliskiren (see also information under the headings “Do not take Roxampex” and “Warnings and precautions”).

Roxampex with food and drink

It is preferable to take Roxampex before a meal.

Pregnancy and breast-feeding

Those who are pregnant or breast-feeding must not take Roxampex.

Pregnancy

Patients must tell their doctor if they think that they are (or might become) pregnant. If a patient becomes pregnant while taking Roxampex, must stop taking it immediately and tell it the doctor. The doctor will normally advise the patient to stop taking Roxampex before becoming pregnant or as soon as she knows she is pregnant and will advise her to take another medicine instead of Roxampex.

Women should avoid becoming pregnant while taking Roxampex by using suitable contraception.

Breast-feeding

Those who are breast-feeding or about to start breast-feeding should consult their doctor. Roxampex is contra-indicated for mothers who are breast-feeding, and the doctor may choose another treatment for the patient if she wishes to breast-feed, especially if her baby is newborn, or was born prematurely.

Driving and using machines

Roxampex may affect the ability to drive or use machines. Patients are advised not to drive a car or operate machinery until they know how Roxampex affects them.

If the tablets make the őatient feel sick, dizzy or tired, or give him/her a headache, the patient must not drive or use machines and should contact the doctor immediately.

How to take Roxampex

The recommended dose is one tablet once a day. The tablet should be preferably taken in the morning and before a meal. It should be swallowed with a glass of water.

The doctor will decide on the correct dose for the given patient. Roxampex is prescribed for patients already taking rosuvastatin, perindopril and amlodipine from separate tablets.

What to do if more Roxampex was taken that it should have been?

Thef doctor or the nearest hospital casualty must be contacted department immediately. The most likely effect in case of overdose is low blood pressure. If marked low blood pressure occurs (symptoms such as dizziness or faintness), lying down with the legs raised can help.

What to do if taking Roxampex was forgotten?

It is important to take this medicine every day as regular treatment is more effective. However, if forgetting to take a dose of Roxampex, the patient should take the next dose at the usual time. No double dose to make up for a forgotten tablet must be taken!

May patients stop taking Roxampex?

As the treatment for high blood pressure is usually life-long, the patient should discuss with the doctor before stopping this medicinal product.

Possible side effects

Like all medicines, Roxampex can cause side effects, although not everybody experiences them.

Patients must stop taking the medicinal product and see a doctor immediately, if experiencing any of the following side effects that can be serious:
- swelling of the face, lips, mouth, tongue or throat, difficulty in swallowing (angioedema) (See section 2 "Warnings and precautions". It is uncommon – may affect up to 1 in 100 people),
- severe dizziness or fainting due to low blood pressure (common – may affect up to 1 in 10 people),
- unusual fast or irregular heartbeat, chest pain (angina) or heart attack (very rare – may affect up to 1 in 10,000 people),
- weakness of arms or legs, or problems speaking which could be sign of a possible stroke (very rare),
- sudden wheeziness, chest pain, shortness of breath, or difficulty in breathing (bronchospasm, uncommon),
- inflamed pancreas which may cause severe abdominal and back pain accompanied with feeling very unwell (rare – may affect up to 1 in 1,000 people),
- yellowing of the skin or eyes (jaundice) which could be a sign of hepatitis (very rare),
- skin rash which often starts with red itchy patches on your face, arms or legs (erythema multiforme, very rare),
- serious skin rashes (Stevens-Johnson syndrome, toxic epidermal necrolysis). These can appear as reddish target-like macules or circular patches often with central blisters on the trunk, skin peeling, ulcers of mouth, throat, nose, genitals and eyes and can be preceded by fever and flu-like symptoms. (very rare).

Also, patients must stop taking Roxampex and talk to their doctor immediately if they have any unusual aches or pains in their muscles which go on for longer than it migth be expected. Muscle symptoms are more common in children and adolescents than in adults. As with other statins, a very small number of people have experienced unpleasant muscle effects and rarely these have gone on to become a potentially life threatening muscle damage known as rhabdomyolysis.

In decreasing order of frequency, side effects can also include the following.

Very common (may affect more than 1 in 10 people): oedema (fluid retention).

Common (may affect up to 1 in 10 people):

- diabetes (this is more likely if the patient has high levels of sugars and fats in the blood, is overweight and has high blood pressure; the doctor will monitor you while the patient is taking this medicine);
- dizziness, headache, vertigo, pins and needles, somnolence;
- palpitations (awareness of the heart beat);
- low blood pressure, flushing;
- cough, shortness of breath;
- gastro-intestinal disorders (taste disturbances, dyspepsia or difficulty of digestion, vomiting, abdominal pain, nausea, diarrhoea, constipation);
- allergic reactions (such as skin rashes, itching);
- vision disturbances (includin double vision);
- tinnitus (sensation of noises in the ears);
- muscle pain, cramps;
- feeling of tiredness, fatigue.

Uncommon (may affect up to 1 in 100 people):
- excess of eosinophils (a type of white blood cells);
- mood swings, sleep disturbances, depression, sleeplessness;
- trembling, numbness or tingling sensation in your limbs, loss of pain sensation, fainting;
- heart rhythm disorders, tachycardia;
- inflammation of blood vessels;
- bronchospasm (tightening of the chest, wheezing and shortness of breath), sneezing/running nose caused by inflammation of the lining of the nose (rhinitis);
- dry mouth;
- angioedema (symptoms such as wheezing, swelling of the face or tongue);
- kidney problems;
- intense itching or severe skin rashes, formation of blister clusters over the skin, hair loss, increased sweating, itchy skin, red patches on skin, skin discolouration;
- photosensitivity reaction (increased sensitivity of the skin to sun);
- joint pain;
- back pain;
- 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;
- chest pain, pain, malaise, oedema peripheral, fever;
- change in laboratory parameters: high blood level of potassium reversible on discontinuation, low level of sodium, hypoglycaemia (very low blood sugar level) in case of diabetic patients, increased blood urea, and increased blood creatinine;
- weight increase or decrease;
- fall.

Rare (may affect up to 1 in 1000 people):
- changes in laboratory parameters: increased level of liver enzymes, high level of serum bilirubin, lower number of blood platelets;
- confusion, damage to the nerves of the legs and arms (such as numbness), memory loss;
- a severe stomach pain (inflamed pancreas);

- severe allergic reaction – signs include swelling of the face, lips, tongue and/or throat, difficulty in swallowing and breathing, a severe itching of the skin (with raised lumps). Those who think they are having an allergic reaction, stop taking Roxampex and seek medical help immediately;
- lupus-like disease syndrome (including rash, joint disorders and effects on blood cells);
- muscle damage in adults, muscle rupture – as a precaution, patient should stop taking Roxampex and talk to the doctor immediately if they have any unusual aches or pains in the muscles which go on for longer than expected.

Very rare (may affect up to 1 in 10,000 people):
- changes in blood values such as a lower number of white and red blood cells, lower haemoglobin;
- excess sugar in blood (hyperglycaemia);
- damage to the nerves of the legs and arms (such as numbness);
- memory loss;
- cardiovascular disorders (angina pectoris and heart attack);
- increased muscle tension;
- eosinophilic pneumonia (a rare type of pneumonia), rhinitis;
- abdominal bloating (gastritis);
- swelling of the gums;
- abnormal liver function, inflammation of the liver (hepatitis), jaundice (yellowing of the skin and eyes);
- erythema multiforme (a skin rash which often starts with red itchy patches on your face, arms or legs);
- Stevens-Johnson syndrome (serious blistering condition of the skin, mouth, eyes and genitals),
- traces of blood in the urine, severe kidney problems.

Concentrated urine (dark in colour), feeling or being sick, having muscle cramps, confusion and fits which may be due to inappropriate ADH (anti-diuretic hormone) secretion can occur with ACE inhibitors.

Not known (frequency cannot be estimated from the available data):
- sleep disturbances, including insomnia and nightmares;
- tendon injury, muscle weakness that is constant;
- redness and peeling of the skin over large areas of the body;
- angioneurotic oedema;
- severe skin reaction (toxic epidermal necrolysis);
- discoloration, numbness and pain in fingers or toes (Raynaud‘s phenomenon).

Disorders of the blood, kidney, liver or pancreas and changes in laboratory parameters (blood tests) can occur. The doctor may need to give the patient blood tests to monitor his/her condition.

How to store Roxampex?

This medicine does not require any special temperature storage conditions. It should be stored in the original package in order to protect from light and kept out of the sight and reach of children.

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Roxampex 10 mg/5 mg/4 mg, 10 mg/5 mg/8 mg, 10 mg/10 mg/8 mg, 20 mg/5 mg/4 mg, 20 mg/5 mg/8 mg, 20 mg/10 mg/8 mg film-coated tablets. The procedure was finalised at 19 September 2019. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, an application has been submitted to the reference and competent authorities of the Member State concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member states, CMS: Bulgaria, Estonia, Finland, Latvia, Lithuania, Poland, Portugal, Romania, the Slovak Republic and Slovenia) concerned the fixed combination of rosuvastatin/amlodipine/perindopril tert-butylamine 10 mg/5 mg/4 mg, 10 mg/5 mg/8 mg, 10 mg/10 mg/8 mg, 20 mg/5 mg/4 mg, 20 mg/5 mg/8 mg, 20 mg/10 mg/8 mg film-coated tablets (Roxampex film-coated tablets, named Rosamera in Bulgaria and Poland).

Based on the review of the quality, safety and efficacy data, the Member States have granted the marketing authorisation for Roxampex 10 mg/5 mg/4 mg, 10 mg /5 mg/8 mg, 10 mg/10 mg /8 mg, 20 mg/5 mg/4 mg, 20 mg/5 mg /8 mg, 20 mg/10 mg /8 mg film-coated tablets from Krka, d.d., Novo mesto

The marketing authorisation has been granted pursuant to Article 10b of Directive 2001/83/EC (fixed dose combination application).

Three bioequivalence studies have been performed between Roxampex and co-administered Prestance (perindopril/amlodipine) and Crestor (rosuvastatin) in accordance with the "Guideline on the investigation of bioavailability and bioequivalence" (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr, 2010).

The product is indicated for substitution therapy in adult patients adequately controlled with rosuvastatin, perindopril and amlodipine taken concomitantly as a single-component rosuvastatin and a dual-component perindopril and amlodipine at the same dose level as in the combination for treatment of hypertension and one of the following coincident conditions:

- primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIb) as an adjunct to diet when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate,
- homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate.

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A comprehensive description of the indications and posology is given in the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

This chemical-pharmaceutical assessment report concerns the application of Roxampex 10 mg/5 mg/4 mg, 10 mg/5 mg/8 mg, 10 mg/10 mg/8 mg, 20 mg/5 mg/8 mg, 20 mg/5 mg/4 mg and 20 mg/10 mg/8 mg film-coated tablets via a decentralized procedure according to Article 10b of Directive 2001/83/EC (i.e a fixed combination). The products have been developed by KRKA d.d Novo mesto.

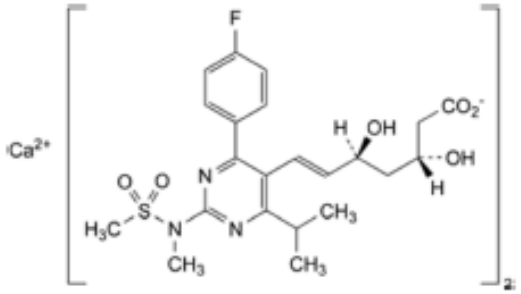
Reference products are Prestance® tablets (perindopril arginine / amlodipine, Les Laboratories Servier) and Crestor® tablets (rosuvastatin, AstraZeneca).

II.2 Drug substances

II.2.1 Rosuvastatin calcium

Data on the quality and manufacture of the drug substance rosuvastatin calcium were provided in the submission using the Active Substance Master File (ASMF) procedure. The Quality Overall Summary is adequate.

INN name: rosuvastatin calcium
Chemical name: **c**alcium (E,3R,5S)-7-[4-(4-fluorophenyl)-2-[methyl(methylsulfonyl) amino]-6-propan-2-ylpyrimidin-5-yl]-3,5-dihydroxyhept-6-enoate.
Structure:



The drug substance is a white to yellowish white or off white hygroscopic powder and is slightly soluble in water, freely soluble in methylene chloride, practically insoluble in anhydrous ethanol. It shows polymorphism, the manufacturer consistently produces the correct isomer and the same polymorphic form.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the drug substance is adequate.

Evidence of the structure has been confirmed by elementary analysis, mass spectra, NMR spectra and by FT-IR spectra. The impurity profile of the substance contains detailed information about genotoxic impurities, residual solvents and catalysts.

The substance is specified according to the requirements of the current European Pharmacopoeia (Ph. Eur.) monograph, supplemented by additional in-house tests.

Testing methods not described in detail in the pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the drug substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

The substance complies with the requirements of the European Medicines Agency (EMA) guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch-to-batch consistency of the production.

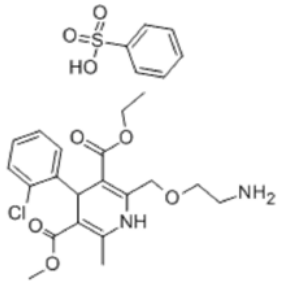
Good Manufacturing Practice (GMP) compliance of the drug substance manufacture is demonstrated by the applicant.

Stability studies have been performed with the drug substance. According to the presented stability data the proposed re-test period is acceptable if stored in a refrigerator (2°C - 8°C) in the original packaging in order to protect from moisture and light.

II.2.2 Amlodipine besilate

Data on the quality and manufacture of the active substance amlodipine besilate were provided in the submission using the Certificate of the European Pharmacopoeia (CEP) procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: amlodipine
Chemical name: 5-methyl-3-ethyl-[(4RS)-2-[(2-aminoethoxy)methyl]-6-methyl-4-(2-chlorophenyl)-1,4- dihydropyridine-3,5-dicarboxylate] benzenesulphonate.
Structure:



The drug substance is a white to almost white powder and is slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol, slightly soluble in 2-propanol.

The substance is specified according to the requirements of the current Ph. Eur. monograph and the CEP, additional specifications have also been set
.
The Ph. Eur. specification includes the following tests for amlodipine besilate: appearance, solubility, identification (IR), optical rotation, related substances (HPLC), water content, sulphated ash, assay (HPLC). Residual solvents (GC) is also controlled (according to the CEP). The specification is in accordance with the Ph. Eur. general monograph on Substances for pharmaceutical use and the International Council on Harmonisation (ICH) Q6A guideline.

Testing methods not described in detail in the pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the drug substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

The substance complies with the requirements of the EMA guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch-to-batch consistency of the production.

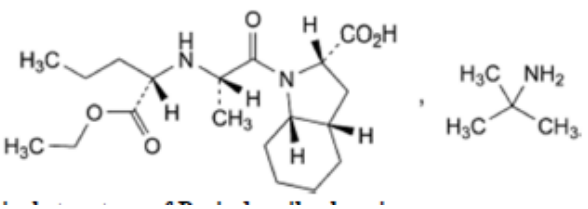
GMP compliance of the drug substance manufacture is demonstrated by the applicant.

A retest period and the packaging material (double polyethylene bag (outer black) placed in either a fibreboard or a polyethylene drum) have been mentioned in the CEP.

II.2.3 Perindopril erbumine

Data on the quality and manufacture of the active substance were provided in the submission using the Active Substance Master File (ASMF) procedure. The Quality Overall Summary is adequate.

INN name: perindopril erbumine
Chemical name: 2-Methylpropan-2-amine(2S,3aS,7aS)-1-((S)-2-((S)-1-ethoxy-1-oxo pentan-2 ylamino)propanoyl)octahydro-1H-indole-2-carboxylate
Structure:



The drug substance is a white or almost white, slightly hygroscopic crystalline powder and is freely soluble in water and in ethanol. It shows polymorphism, the manufacturer consistently produces the correct isomer and the same polymorphic form.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the drug substance is adequate.

Evidence of the structure has been confirmed by elementary analysis, mass spectra, NMR spectra and by FT-IR spectra. The impurity profile of the substance contains detailed information about genotoxic impurities, residual solvents and catalysts.

The substance is specified according to the requirements of the current Ph. Eur. monograph, additional specifications have also been set.

The Ph. Eur. specification includes the following tests for perindopril erbumine: appearance, solubility, identification (specific optical rotation, IR, TLC), impurity A (TLC), stereochemical purity (HPLC), related substances (HPLC), water content, sulphated ash and assay (titration). The specification is in accordance with the Ph. Eur. general monograph on Substances for pharmaceutical use and the ICH Q6A guideline.

Testing methods not described in detail in the pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the drug susbtance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

The substance complies with the requirements of the EMA guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch-to-batch consistency of the production.

Stability studies have been performed with the drug substance. According to the presented stability data the proposed re-test period of is acceptable with the following storage restriction: “Do not store above 25°C. Store in the original packaging”.

GMP compliance of the drug substance manufacture is demonstrated by the applicant.

II.3 Medicinal product

The aim of the development was to develop a combination product with perindopril erbumine, amlodipine and rosuvastatin in a single tablet to support patient adherence to treatment, which is bioequivalent to the co-administered reference products: Prestance® tablets (containing perindopril and amlodipine) (Servier) and Crestor® (rosuvastatin) film-coated tablets (AstraZeneca).

A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

As regards dissolution and impurity profile the product is shown to be similar to the reference products.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance, composition and packaging was obtained.

10 mg/5 mg/4 mg: off-pink, round, slightly biconvex, film-coated tablets with bevelled edges, engraved with mark PAR1 on one side of the tablet (tablet diameter: approximately 8.5 mm).
10 mg/5 mg/8 mg: pale pinkish-brown, round, slightly biconvex, film-coated tablets with bevelled edges, engraved with mark PAR2 on one side of the tablet (tablet diameter: approximately 8.5 mm).
10 mg/10 mg/8 mg: yellowish brown, round, slightly biconvex, film-coated tablets with bevelled edges, engraved with mark PAR3 on one side of the tablet (tablet diameter: approximately 11 mm).
20 mg/5 mg/4 mg: light orange pink, round, slightly biconvex, film-coated tablets with bevelled edges, engraved with mark PAR4 on one side of the tablet (tablet diameter: approximately 11 mm).
20 mg/5 mg/8 mg: light yellow, round, slightly biconvex, film-coated tablets with bevelled edges, engraved with mark PAR5 on one side of the tablet (tablet diameter: approximately 11 mm).
20 mg/10 mg/8 mg: white, round, slightly biconvex, film-coated tablets with bevelled edges, engraved with mark PAR6 on one side of the tablet (tablet diameter: approximately 11 mm).

The excipients used in the finished products are microcrystalline cellulose, crospovidone (type A), colloidal anhydrous silica, magnesium stearate and film-coating (polyvinyl alcohol, macrogol 3350, titanium dioxide (E171), red/yellow/black iron-oxide (E172) and talc. All excipients used comply with their respective Ph. Eur. monograph. Compliance of the product with the general monograph of the Ph. Eur. on the Products with the risk of TSE has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence studies are presented.

The container closure system of the product is OPA/Al/PVC//Al blister. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 2 years is approved with the following storage restriction: "Store in the original package in order to protect from light. This medicinal product does not require any special temperature storage conditions."

The Summary of Product Characteristics, Package Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

From chemical-pharmaceutical points of view the product is approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Roxampex is a combination of rosuvastatin, a selective and competitive inhibitor of HMG-CoA reductase, amlodipine, a calcium antagonist, and perindopril tert-butylamine salt, an angiotensin-converting enzyme inhibitor. Its properties are derived from those of each of the components separately.

Pharmacodynamic, pharmacokinetic and toxicological properties of perindopril, amlodipine and rosuvastatin are well known. No further non-clinical studies are required. The non-clinical overview is therefore based on a review of data available in several scientific databases or published in relation to the active ingredients.

Overview based on literature review is appropriate.

III.2 Pharmacology

Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor for cholesterol. The primary site of action of rosuvastatin is the liver, the target organ for cholesterol lowering.

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.

Perindopril is an inhibitor of the angiotensin converting enzyme (ACE inhibitor) which converts angiotensin I to angiotensin II, a vasoconstricting substance; in addition the enzyme stimulates the secretion of aldosterone by the adrenal cortex and stimulates the degradation of bradykinin, a vasodilatory substance, into inactive heptapeptides.

III.3 Pharmacokinetics

No new non-clinical pharmacokinetic studies were conducted by the applicant.

Rosuvastatin is taken up extensively by the liver which is the primary site of cholesterol synthesis and LDL-cholesterol clearance. It is mainly bound to plasma proteins. Rosuvastatin undergoes limited metabolism. In vitro metabolism studies using human hepatocytes indicate that rosuvastatin is a poor substrate for cytochrome P450-based metabolism. CYP2C9 was the principal isoenzyme involved, with 2C19, 3A4 and 2D6 involved to a lesser extent. The main

metabolites identified are the N-desmethyl and lactone metabolites. The N-desmethyl metabolite is approximately 50% less active than rosuvastatin whereas the lactone form is considered clinically inactive. Rosuvastatin dose is mostly excreted unchanged in the faeces (consisting of absorbed and non-absorbed active substance) and the remaining part is excreted in urine.

After oral administration of therapeutic doses, *amlodipine* is well absorbed. It is extensively metabolised by the liver to inactive metabolites.

After oral administration, the absorption of *perindopril* is rapid. Perindopril is a prodrug. Twenty seven percent of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. In addition to active perindoprilat, perindopril yields five metabolites, all inactive. Perindoprilat is eliminated in the urine

III.4 Toxicology

No new toxicity studies were submitted by the applicant for the product, which is acceptable for this type of application.

Non-clinical data on *rosuvastatin* reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenicity potential. In repeated-dose toxicity studies histopathologic liver changes likely due to the pharmacologic action of rosuvastatin were observed in mouse, rat, and to a lesser extent with effects in the gall bladder in dogs, but not in monkeys. In addition, testicular toxicity was observed in monkeys and dogs at higher dosages. Reproductive toxicity was evident in rats, where systemic exposures were several times above the therapeutic exposure level.

Regarding *amlodipine*, 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. 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. 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.

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

With regard to *perindopril,* in the chronic oral toxicity studies (rats and monkeys), the target organ is the kidney, with reversible damage. No mutagenicity has been observed in in vitro or *in vivo* studies. Reproduction toxicology studies (rats, mice, rabbits, and monkeys) showed no

sign of embryotoxicity or teratogenicity. No carcinogenicity has been observed in long term studies in rats and mice.

III.5 Ecotoxicology/environmental risk assessment

Since the combination products Roxampex are intended for substitution indication and, as such, they will replace use of the co-administered perindopril, amlodipine and rosuvastatin, this will not lead to an increased exposure to the environment.

An environmental risk assessment therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

Abridged applications avoid the need for repetitive tests on animals. Pharmacodynamics, pharmacokinetics and toxicology of perindopril, amlodipine and rosuvastatin are well-known. As the co-administration of perindopril, amlodipine and rosuvastatin is also well known, there is no need for further excessive non-clinical studies. Overviews on the non-clinical characteristics of the three active substances of Roxampex have been adequately included.

From non-clinical points of view the product is approvable.

IV. CLINICAL ASPECTS

IV.1 Introduction

Pharmacodynamics, pharmacokinetics, efficacy and safety of the monocomponents are well established.

To support the application, the applicant submitted three bioequivalence studies. Moreover, the application contains an adequate review of published clinical data.

IV.2 Pharmacokinetics

IV.2.1 Literature data

Basic pharmacokinetic properties of perindopril, amlodipine and rosuvastatin were overviewed by the applicant.

According to the presented clinical and literature data no clinically relevant pharmacokinetic interaction can be expected between co-administered active substances.

Maximum *rosuvastatin* plasma concentrations are achieved approximately 5 hours after oral administration. The absolute bioavailability is approximately 20%. Rosuvastatin is taken up extensively by the liver which is the primary site of cholesterol synthesis and LDL-C clearance. Approximately 90% of rosuvastatin is bound to plasma proteins, mainly to albumin. Rosuvastatin undergoes limited metabolism (approximately 10%). Approximately 90% of the rosuvastatin dose is excreted unchanged in the faeces (consisting of absorbed and non-absorbed active substance) and the remaining part is excreted in urine.

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 bioavailability of amlodipine is not affected by food intake. In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine. The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing.

Perindopril is a prodrug. After oral administration, the absorption of perindopril is rapid and the peak concentration is achieved within 1 hour. The plasma half-life of perindopril is equal to 1 hour. Twenty seven percent of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. Protein binding of perindoprilat

to plasma proteins is 20%, principally to angiotensin converting enzyme, but is concentration dependent. In addition to active perindoprilat, perindopril yields five metabolites, all inactive. As ingestion of food decreases conversion to perindoprilat, hence bioavailability, perindopril tert-butylamine should be administered orally in a single daily dose in the morning before a meal. Perindoprilat is eliminated in the urine and the terminal half-life of the unbound fraction is approximately 17 hours, resulting in steady-state within 4 days.

IV.2.2 Bioequivalence studies

Three bioequivalence studies were performed, and biowaiver claim was submitted for the lower strengths (perindopril/ amlodipine/ rosuvastatin 8 mg/5mg/20 mg, 8 mg/10mg/10mg and 4 mg/ 5mg/10mg). As per the general criteria outlined in the Guideline on the *Investigation of Bioequivalence* were fulfilled the biowaiver request for the above mentioned strengths are acceptable.

By the Sponsor's statement the studies were conducted in compliance with the requirements of guideline on *Good Clinical Practice* ICH Topic E6 (R1), CPMP/ICH/135/95, Guideline on *the investigation of bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, January 2010) and ethical principles stated in the last revision of Declaration of Helsinki.

Bioequivalence was concluded if the 90% confidence intervals of the ratio (Test/Reference) of least-squares means of the ln-transformed C_{max}, AUC parameters for rosuvastatin, amlodipine and perindopril were included within the interval 80.00-125.00%.

Bioequivalence study with the 20 mg/10 mg/8 mg strengths

A bioequivalence study was conducted between rosuvastatin/amlodipine/perindopril/ 20 mg/10 mg/8 mg film-coated tablets (Test product, manufacturer: Krka, d.d., Novo mesto) and the Reference medication: Prestance® 10 mg/10 mg tablets (perindopril/amlodipine, corresponding, because of the different arginine salt form of perindopril, to the 10 mg/8 mg strength of the Test product) concomitantly given with Crestor® 20 mg film-coated tablets (rosuvastatin-calcium) in healthy volunteers under fasting conditions.

The results were as follows:

Pharmacokinetic parameter	Geometric Mean Ratio% Test/Reference	Confidence interval %	CV%
Rosuvastatin			
AUC_{0-t}	99.89	93.95 – 106.20	17.8
C_{max}	98.30	90.44 – 106.84	24.4
Amlodipine			
AUC_{0-t}	103.59	101.21 – 106.03	6.7
C_{max}	102.13	97.95 – 106.49	12.3

Perindopril			
AUC_{0-t}	94.45	91.58 – 97.41	8.9
C_{max}	99.64	93.55 – 106.12	18.3

Bioequivalence study with the 20 mg/5 mg/4 mg strengths

The study was performed between rosuvastatin/ amlodipine/perindopril 20 mg/ 5 mg/4 mg film-coated tablets (Test product, manufacturer: Krka, d.d., Novo mesto) and Prestance® 5 mg/ 5 mg tablets concomitantly given with Crestor® 20 mg film-coated tablets (rosuvastatin-calcium) as Reference medication in healthy volunteers under fasting conditions.

The results were as follows:

Pharmacokinetic parameter	Geometric Mean Ratio% Test/Reference	Confidence interval %	CV%
Rosuvastatin			
AUC_{0-t}	97.22	91.81 – 102.95	15.9
C_{max}	97.18	88.70 – 106.46	25.5
Amlodipine			
AUC_{0-t}	101.90	99.37 – 104.50	6.9
C_{max}	100.80	97.95 – 103.74	7.9
Perindopril			
AUC_{0-t}	92.54	90.21 – 94.94	7.0
C_{max}	92.23	88.10 – 96.56	12.7

Bioequivalence study with the 10 mg/5 mg/8 mg strengths

The study was performed between rosuvastatin/ amlodipine/perindopril 10 mg/5 mg/8 mg film-coated tablets (Test product, manufacturer: Krka, d.d., Novo mesto) and Prestance® 10 mg/5 mg tablets concomitantly given with Crestor® 10 mg film-coated tablets (rosuvastatin-calcium) as Reference medication in healthy volunteers under fasting conditions.

The results were as follows:

Pharmacokinetic parameter	Geometric Mean Ratio% Test/Reference	Confidence interval %	CV%
Rosuvastatin			
AUC_{0-t}	97.66	90.99 – 104.81	20.4
C_{max}	99.66	90.04 – 110. 32	29.6
Amlodipine			
AUC_{0-t}	99.46	95.47 – 101.62	11.7
C_{max}	100.94	96.35 – 105.74	13.3
Perindopril			

AUC_{0-t}	92.94	88.72 – 97.37	11.3
C_{max}	91.24	82.54 – 100.86	29.2

Conclusion of the performed bioequivalence studies

Based on the results of the three demonstrated pivotal studies Roxampex 20 mg/10 mg/8 mg, 20 mg/5 mg/4 mg, 10 mg/5 mg/8 mg film-coated tablets were considered bioequivalent with the appropriate concomitantly given Reference products (Prestance® 10 mg/10 mg, 5 mg/5mg, 10 mg/5 mg tablets, respectively, and Crestor® 20 mg or 10 mg film-coated tablets) in healthy adult volunteers under fasting conditions.

Biowaiver

The applicant has submitted biowaiver request for the 20 mg/5 mg/8 mg, 10 mg/10 mg/8 mg and 10 mg/5 mg/4 mg strengths. In accordance with the Guideline on the Investigation of Bioequivalence the successfully performed bioequivalence study with the highest strength (8mg/ 10mg/ 20mg) is possible to be used to waive additional clinical studies.

As the general criteria outlined in the Guideline have been fulfilled (same manufacturer, same manufacturing process, dose-proportional quantitative and same qualitative composition), similar dissolution profiles were demonstrated and rosuvastatin, amlodipine and perindopril show linear pharmacokinetic in the claimed dose range, the biowaiver request for the claimed strengths can be accepted.

Further studies

The submitted literature data did not close the possibility of interaction between *amlodipine – rosuvastatin* and *perindopril – rosuvastatin*, hence further *in vitro*/*in vivo* data were requested to provide that the pharmacokinetic profiles (AUC and also C_{max}) of the monocomponents are unequivocally not affected by their combination.

Four Extrinsic Factor pharmacokinetic study reports for showing the possible drug-drug interaction were designed to exclude all potential confounding factors.

One study investigated the impact of perindopril on rosuvastatin, the second investigated the impact of rosuvastatin on perindopril and perindoprilat, the third one investigated the impact of amlodipine on rosuvastatin and the last one investigated the impact of rosuvastatin on amlodipine.

As per the conducted studies it can be concluded that perindopril has no impact on rosuvastatin pharmacokinetics and rosuvastatin has no impact on amlodipine pharmacokinetics, furthermore, rosuvastatin does not affect the pharmacokinetic parameters of perindoprilat (active metabolite of perindopril).

IV.3 Pharmacodynamics

Perindopril, amlodipine and rosuvastatin are well-known active substances with established pharmacodynamics. No new own pharmacodynamic studies were provided and none were deemed necessary.

IV.4 Clinical efficacy

The applicant summarized the efficacy of the monocomponents as well as the recommendations of therapeutic guidelines about their concomitant use and provided data on efficacy of the combination.

Furthermore, co-prescription data were submitted for each strength separately.

The totality of data is considered sufficient to support the efficacy of the combination.

IV.5 Clinical safety

Safety profiles of the monocomponents are well known and were summarized in the overview. The applicant provided also safety data with the combination. Furthermore, safety data from the bioequivalence studies were submitted.

Safety data do not indicate any new safety concerns.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance System

The applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the legal requirements as set out in the Commission Implementing Regulation and as detailed in the Good Pharmacovigilance Practices module, the RMS considers the Summary acceptable.

IV.6.2 Risk Management Plan

The applicant has submitted a Risk Management Plan in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Roxampex film-coated tablets.

The applicant has identified the following safety concerns

Summary of safety concerns	
Important identified risks	- Skeletal muscle effects: rhabdomyolysis, myopathy, myositis, myalgia, creatine kinase increases, immune-mediated necrotising myopathy. - Hepatic effects: permanently increased transaminases, hepatitis, jaundice, hepatic impairment. - Drug interactions: drug-drug interactions including: ciclosporin, various protease inhibitors with ritonavir, gemfibrozil, clopidogrel, eltrombopag, dronedarone, warfarin and other vitamin K antagonists, fusidic acid and ezetimibe. - Hypersensitivity reactions (including angioedema, intestinal angioedema, concomitant use of mTOR inhibitor, photosensitivity and anaphylactoid reactions). - Hypotension. - Renal dysfunction, hypotension, and hyperkalaemia as consequence of dual RAAS blockade. - Use in pregnancy and breastfeeding.
Important potential risks	- Renal effects: renal failure (including acute and chronic renal failure) and renal impairment. - Interstitial lung disease. - Off label use.
Missing information	- Use in children and adolescents. - Lack of safety data on long-term use of the combination.

Pharmacovigilance Plan: routine pharmacovigilance activities are considered sufficient to manage all safety concerns connected to Roxampex film-coated tablets. No additional activities are proposed.

Risk Minimisation Measures: routine measures (i.e. wording in Summary of Product Characteristics Package Leaflet and classification as a prescription-only medicine) are considered sufficient to manage all safety concerns connected to Roxampex film-coated tablets. No additional activities are proposed. For any further information on risk minimisation, please refer to the product information.

IV.6.3 Periodic Safety Update Reports

Rosuvastatin/amlodipine/perindopril combination is currently not included in the list published by the EMA. Taking into account the Periodic Safety Update Report (PSUR) cycle of similar combination product (atorvastatin/amlodipine//perindopril, its PSUR cycle is 5 years), the RMS suggests the following. The marketing authorisation holder (MAH) shall submit the first periodic safety update report for this product with a period of 5 years following authorisation. Further, MAHs shall continuously check the European medicines web-portal if the active substance has been included in the list of Union

reference dates (EURD list). If yes, after publication in the EURD list the PSURs shall be submitted in accordance with the requirements set out in the EURD list.

IV.7 Discussion on the clinical aspects

Abridged applications avoid the need for repetitive tests on humans. For these applications, the bioequivalence studies described in section IV.2 are pivotal.

The applicant demonstrated bioequivalence between the combination and co-administered reference products containing the active ingredients in the same strengths.

The application for these combination products contains an adequate review of published clinical data.

Overall, the provided clinical overview is considered sufficient to support this combination.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present applications concern Roxampex 10 mg/5 mg/4 mg, 10 mg/5 mg/8 mg, 10 mg/10 mg/8 mg, 20 mg/5 mg/ 4 mg, 20 mg/5 mg/8 mg and 20 mg/10 mg/8 mg film-coated tablets, fixed combinations of rosuvastatin/amlodipine/perindopril,. The applicant and the future holder of authorisation is Krka d.d., Novo mesto, Slovenia.

The products are indicated for substitution therapy in adult patients adequately controlled with rosuvastatin, perindopril and amlodipine taken concomitantly as a single-component rosuvastatin and a dual-component perindopril and amlodipine at the same dose level as in the combination for treatment of hypertension and one of the following coincident conditions:

- primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIb) as an adjunct to diet when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate,
- homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate.

The application for these combination products contains an adequate review of published non-clinical and clinical data. Moreover, to support the application the applicant demonstrated bioequivalence between the combination and co-administered two marketed “reference” products that contained the active components of the combinations in corresponding strengths: Prestance (perindopril/amlodipine) and Crestor (rosuvastatin).

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised.

The therapeutic benefit/risk assessment is, therefore, positive.

Based on the review of the quality, safety and efficacy data, the Member States have granted the marketing authorisation for Roxampex 10 mg/5 mg/4 mg, 10 mg /5 mg/8 mg, 10 mg/10 mg /8 mg, 20 mg/5 mg/4 mg, 20 mg/5 mg /8 mg, 20 mg/10 mg /8 mg film-coated tablets from Krka, d.d., Novo mesto

V.2 Classification

Prescription-only medicine.

V.3 Package Leaflet and user consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the patient information leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. Upgrade: steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached
IB B.II.f.t.b.1. Extension of the shelf-life of the product, based on real-time data, from 24 to 36 months	HU/H/0598/001-006/IB/001	yes	06. 11. 2019	06. 12. 2019	approval	no