OGYÉI
National Institute of
Pharmacy and Nutrition

H-1051 Budapest, Zrínyi u. 3.
1372 P.O. Box:450.
Tel: +36 1 88 69-300, Fax: +36 1 88 69 460
E-mail: ogyei@ogyei.gov.hu, Web: www.ogyei.gov.hu

Public Assessment Report

Name of the Product:

Roxiper

10 mg/4 mg/1.25 mg, 20 mg/4 mg/1.25 mg, 10 mg/8 mg/2.5 mg, 20 mg/8 mg/2.5 mg film-coated tablets

(rosuvastatin/perindopril tert-butylamine/indapamide)

Procedure number: HU/H/0484/001-004/DC

Marketing authorisation holder: Krka d.d.

Date: 15 February 2019

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Roxiper 10 mg/4 mg/1.25 mg, 20 mg/4 mg/1.25 mg, 10 mg/8 mg/2.5 mg, 20 mg/8 mg/2.5 mg film-coated tablets. The holder of the marketing authorisation is Krka d.d., Novo mesto, Slovenia.

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

Each Roxiter 10 mg/4 mg/1.25 mg film-coated tablet contains 10 mg rosuvastatin (as rosuvastatin calcium), 4 mg perindopril tert-butylamine and 1.25 mg indapamide.

Each Roxiter 20 mg/4 mg/1.25 mg film-coated tablet contains 20 mg rosuvastatin (as rosuvastatin calcium), 4 mg perindopril tert-butylamine and 1.25 mg indapamide.

Each Roxiter 10 mg/8 mg/2.5 mg film-coated tablet contains 10 mg rosuvastatin (as rosuvastatin calcium), 8 mg perindopril tert-butylamine and 2.5 mg indapamide.

Each Roxiter 20 mg/8 mg/2.5 mg film-coated tablet contains 20 mg rosuvastatin (as rosuvastatin calcium), 8 mg perindopril tert-butylamine and 2.5 mg indapamide.

The other ingredients (excipients) are:
- tablet core: microcrystalline cellulose (type 200 LM), microcrystalline cellulose (type 112), crospovidone (type A), colloidal anhydrous silica and magnesium stearate (E470b)
- film-coating:
  - the 10 mg/4 mg/1.25 mg, 20 mg/4 mg/1.25 mg and 20 mg/8 mg/2.5 mg film-coated tablets: poly(vinyl alcohol), titanium dioxide (E171), macrogol 3350, talc, red iron oxide (E172), black iron oxide (E172) and yellow iron oxide (E172);
  - the 10 mg/8 mg/2.5 mg film-coated tablets: poly(vinyl alcohol), titanium dioxide (E171), macrogol 3350, talc and red iron oxide (E172).

The 10 mg/4 mg/1.25 mg film-coated tablets are reddish-brown, round, slightly biconvex tablets with bevelled edges, engraved with mark PIR1 on one side of the tablet. Diameter: approximately 7.5 mm (defined by punches).

The 20 mg/4 mg/1.25 mg film-coated tablets are off-pink, round, slightly biconvex tablets with bevelled edges, engraved with mark PIR2 on one side of the tablet. Diameter: approximately 10 mm (defined by punches).

The 10 mg/8 mg/2.5 mg film-coated tablets are light pink, round, slightly biconvex tablets with bevelled edges, engraved with mark PIR3 on one side of the tablet. Diameter: approximately 10 mm (defined by punches).

The 20 mg/8 mg/2.5 mg film-coated tablets are pale pinkish-brown, round, slightly biconvex

film-coated tablets with bevelled edges, engraved with mark PIR4 on one side of the tablet. Diameter: approximately 10 mm (defined by punches).

Roxiper film-coated tablets (further on: Roxiper) are is available in blister packs.

Roxiper is a combination of three active ingredients rosuvastatin, perindopril and indapamide.

Rosuvastatin belongs to a group of medicines called statins. Perindopril is an ACE (angiotensin converting enzyme) inhibitor. Indapamide is a diuretic.

Rosuvastatin help to control high cholesterol level. Perindopril and indapamide help to control high blood pressure (hypertension).

Roxiper is prescribed for treatment of high blood pressure (hypertension) and concomitant high cholesterol level. Patients already taking rosuvastatin, perindopril and indapamide from separate tablets may instead receive one tablet of Roxiper which contains all three ingredients.

What patients need to know before taking Roxiper

Those who
- allergic to rosuvastatin, to perindopril or any other ACE inhibitor, to indapamide or any other sulphonamides, or any of the other ingredients of Roxiper;
- 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 they 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 low blood potassium;
- are suspected of having untreated decompensated heart failure (severe water retention, difficulty in breathing);
- have a severe kidney disease or if are receiving dialysis;
- have liver disease or suffer from a condition called hepatic encephalopathy (disease of the brain caused by liver illness);
- have repeated or unexplained muscle aches or pains;
- take a medicine called ciclosporin (used, for example, after organ transplants);
- are pregnant or breast-feeding. If becoming pregnant while taking Roxiper, stop taking it immediately and consult the doctor (women should avoid becoming pregnant while taking Roxiper by using suitable contraception)

should not take Roxiper.

Warnings and precautions

The doctor should be consulted before taking Roxiper if the patient
- has 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);
- has any other heart problems or problems with your kidneys;
- has kidney problems;
- has liver problems;
- suffers from a collagen disease (skin disease) such as systemic lupus erythematosus or scleroderma;
- has severe respiratory failure;
- has too much acid in blood, which may cause an increased rate of breathing;
- has 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, (then the treatment should be terminated immediately and the doctor contacted directly);
- had photosensitivity reactions;
- is on a salt restricted diet or use salt substitutes which contain potassium;
- takes lithium or potassium-sparing diuretics (spironolactone, triamterene) as their use with Roxiper should be avoided (see "Taking other medicines");
- suffers from hyperparathyroidism (overactive parathyroid gland);
- suffers from gout;
- is elderly and the dose needs to be increased;
- has diabetes;
- his/her thyroid gland is not working properly;
- has atherosclerosis (hardening of the arteries);
- is of Asian origin – that is Japanese, Chinese, Filipino, Vietnamese, Korean and Indian. The doctor needs to choose the right start dose of perindopril, indapamide and rosuvastatin to suit to the patient;
- is black people, for those may have higher incidence of angioedema (swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing) and less effective in lowering blood pressure;
- has 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. The doctor should be contacted immediately if the patient has unexplained muscle aches or pains especially if feeling unwell or having a fever. The same is valid if the patient has a muscle weakness that is constant;
- takes other medicines called fibrates to lower the cholesterol or any other medicine used to lower cholesterol (such as ezetimibe). This leaflet should be read carefully, even if haing taken other medicines for high cholesterol before;
- takes medicines used to fight the HIV infection e.g. ritonavir with lopinavir and/or atazanavir, see "Taking other medicines";
- regularly drinks large amounts of alcohol;
- is 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.

  The doctor may check the kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in your blood at regular intervals;
- is 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).

If the patient is taking any of the following medicines, the risk of angioedema is 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).

The patient must tell the doctor if she thinks that she is (or might become) pregnant. Roxiper 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").

When patients are taking Roxiper, they should also inform their doctor or the medical staff if they:
- are to undergo anaesthesia and/or surgery;
- have recently suffered from diarrhoea or vomiting, or are dehydrated;
- are to undergo dialysis or 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;
- are to undergo a medical test that requires injection of an iodinated contrast agent (a substance that makes organs like kidney or stomach visible on an X-ray).

Athletes should be aware that Roxiper contains an active ingredient (indapamide) which may give a positive reaction in drug tests.

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, the doctor will usually carry out this blood test (liver function test) before and during treatment with Roxiper.

While the patients are on this medicine the doctor will monitor them closely if they have diabetes or are at risk of developing diabetes. Patients are likely to be at risk of developing diabetes if they have high levels of sugars and fats in the blood, are overweight and have high blood pressure.

Children and adolescents

Roxiper should not be used in children and adolescents.

Other medicines and Roxiper

Patients must tell their doctor if they are taking, have recently taken or might take any other medicines.

Taking Roxiper should be avoided together with:

- lithium (used to treat depression);
- aliskiren (medicines used to treat hypertension);
- potassium-sparing diuretics (spironolactone, triamterene), potassium salts.

Treatment with Roxiper can be affected by other medicines. The doctor should be consulted if taking any of the following medicines as special care may be required. Such medicines are:
- other medicines for treating high blood pressure, including diuretics (medicines which increase the amount of urine produced by the kidneys);
- procainamide (for the treatment of an irregular heart beat);
- quinidine, hydroquinidine, disopyramide, amiodarone, sotalol (medicines used for heart rhythm problems);
- allopurinol (for the treatment of gout);
- terfenadine or astemizole (antihistamines for hay fever or allergies);
- corticosteroids used to treat various conditions including severe asthma and rheumatoid arthritis,
- tetracosactide (to treat Crohn's disease);
- immunosuppressants used for the treatment of auto-immune disorders or following transplant surgery to prevent rejection (e.g. ciclosporin);
- fluconazole, ketoconazole (anti-fungal medicines);
- rifampicin, erythromycin, clarithromycin (antibiotics);
- halofantrine (used to treat certain types of malaria);
- pentamidine (used to treat pneumonia);
- injectable gold (used to treat rheumatoid polyarthritis);
- vincamine (used to treat symptomatic cognitive disorders in elderly including memory loss);
- bepridil, verapamil, diltiazem (heart medicines);
- benzamides (for the treatment of psychoses);
- digoxin or other cardiac glycosides (for the treatment of heart problems);
- baclofen (to treat muscle stiffness occurring in diseases such as multiple sclerosis);
- medicines to treat diabetes such as insulin or metformin;
- calcium, including calcium supplements;
- stimulant laxatives (e.g. senna);
- non-steroidal anti-inflammatory drugs (e.g. ibuprofen) or high dose salicylates (e.g. aspirin);
- amphotericin B by injection (to treat severe fungal disease);
- medicines to treat mental disorders such as depression, anxiety, schizophrenia…(e.g. tricyclic antidepressants, neuroleptics);
- anaestetics;
- warfarin, 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 your stomach);
- an oral contraceptive (the pill) or hormone replacement therapy;
- ritonavir with lopinavir and/or atazanavir or simeprevir (used to fight the HIV or hepatitis C infection –see "Warnings and precautions";
- 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".
- If patients need to take oral fusidic acid to treat a bacterial infection they 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). See more information regarding rhabdomyolysis in section “Possible side effects”.

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

Roxiper with food and drink

It is preferable to take Roxiper before a meal.

Pregnancy and breast-feeding

Those who are pregnant or breast-feeding should not take Roxiper.

Pregnancy

Those who think that they are (or might become) pregnant must consult their doctor. Those who become pregnant while taking Roxiper, and tell it their doctor. The doctor will normally advise to stop taking Roxiper before the patient become pregnant or as soon as she knows she is pregnant and will advise her to take another medicine instead of Roxiper.

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

Breast-feeding

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

Driving and using machines

Roxiper does not affect alertness but the patient might experience dizziness or weakness due to low blood pressure which could affect the ability to drive or operate machinery. Patients are advised not to drive a car or operate machinery until they know how Roxiper affects them.

How to take Roxiper

The recommended dose is one tablet once a day. It should preferably be 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 each patient. Roxiper is prescribed for patients already taking rosuvastatin, perindopril and indapamide from separate tablets.

What to do if more Roxiper has been taken than it should have been?

In the case too many tablets have been taken, the doctor or the nearest hospital casualty department must be contacted 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 Roxiper has been forgotten?

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

May patients stop taking Roxiper?

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

Possible side effects

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

Patients who experience any of the following, stop taking the medicinal product at once and tell their doctor immediately:
- difficulty in breathing, with or without swelling of the face, lips, tongue and/or throat;
- swelling of the face, lips, tongue and/or throat, which may cause difficulty in swallowing;
- severe dizziness or fainting;
- unusual fast or irregular heart beat;
- severe itching of the skin (with raised lumps).

Also, patients must stop taking Roxiper and talk to their doctor immediately if having any unusual aches or pains in their muscles which go on for longer thanthey might expect. 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 include the following.

Common (may affect up to 1 in 10 people):
- diabetes (this is more likely if you have high levels of sugars and fats in the blood, are overweight and have high blood pressure; the doctor will monitor the patient while taking this medicine);
- dizziness, headache, vertigo, pins and needles;
- vision disturbances (includin double vision);
- tinnitus (sensation of noises in the ears);
- light-headedness due to low blood pressure;
- shortness of breath, cough;
- gastro-intestinal disorders (dry mouth, taste disturbances, epigastric pain, dyspepsia or difficulty of digestion, anorexia, vomiting, abdominal pain, nausea, diarrhoea, constipation);
- allergic reactions (such as skin rashes, itching);
- muscle pain, cramps;
- feeling of tiredness.

Uncommon (may affect up to 1 in 100 people):
- mood swings, sleep disturbances;
- bronchospasm (tightening of the chest, wheezing and shortness of breath);
- angioedema (symptoms such as wheezing, swelling of the face or tongue), urticaria, purpura (red pinpoints on skin). If the patient suffers from systemic lupus erythematous (a type of collagen disease), this might get worse;
- kidney problems;
- inability to obtain an erection;
- sweating;
- an increase in the amount of protein in the urine – this usually returns to normal on its own without having to stop taking Roxiper.

Rare (may affect up to 1 in 1000 people):
- decrease in the number of platelets (which causes easy bruising and nasal bleeding);
- changes in laboratory parameters;
- a severe stomach pain (inflamed pancreas);
- increased level of liver enzymes;
- 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, then stop taking Roxiper and seek medical help immediately;
- muscle damage in adults – as a precaution, taking Roxiper must be stopped and the doctor consulted immediately if having 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):
- decreased numbers of white blood cells, anaemia (decrease in red blood cells);
- confusion, damage to the nerves of your legs and arms (such as numbness), memory loss;

- cardiovascular disorders (irregular heartbeat, angina pectoris and heart attack);
- eosinophilic pneumonia (a rare type of pneumonia), rhinitis;
- 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), photosensitivity reactions (change in skin appearance) after exposure to the sun or artificial UVA;
- joint pain;
- traces of blood in your urine;
- severe kidney problems;
- gynecomastia (breast enlargement in men).

Not known (frequency cannot be estimated from the available data):
- depression;
- fainting;
- sleep disturbances, including insomnia and nightmares;
- diarrhoea (loose stools);
- hepatic encephalopathy (disease of the brain caused by liver illness);
- Stevens-Johnson syndrome (serious blistering condition of the skin, mouth, eyes and genitals);
- muscle weakness that is constant, tendon injury;
- oedema (swelling);
- abnormal ECG heart tracing, life-threatening irregular beat (Torsades de Pointes).

Disorders of the blood, kidney, liver or pancreas and changes in laboratory parameters (blood tests) can also occur. The doctor may need to perform blood tests to monitor the patient's condition.

How to store Roxiper

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

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Roxiper 10 mg/4 mg/1.25 mg, 20 mg/4 mg/1.25 mg, 10 mg/8 mg/2.5 mg, 20 mg/8 mg/2.5 mg film-coated tablets. The procedure was finalised at 25 July 2018. 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 states 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 dose combinations of rosuvastatin/perindopril tert-butylamine/indapamide 10 mg/4 mg/1.25 mg, 20 mg/4 mg/1.25 mg, 10 mg/8 mg/ 2.5 mg, 20 mg/8 mg/2.5 mg film-coated tablets (Roxiper tablets, named Triemma in Latvia).

Three bioequivalence studies have been performed between Roxiper and co-administered Bionoliprel (perindopril arginine/indapamide) and Crestor (rosuvastatin) in accordance with the "*Guideline on the investigation of bioavailability and bioequivalence*" (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr, 2010). Furthermore the applicant submitted a pharmacokinetic interaction study between rosuvastatin and perindopril/indapamide.

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Roxiper 10 mg/4 mg/1.25 mg, 20 mg/4 mg/1.25 mg, 10 mg/8 mg/ 2.5 mg, 20 mg/8 mg/2.5 mg film-coated tablets from Krka, d.d., Novo mesto, Slovenia.

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

The products are indicated for substitution therapy in adult patients adequately controlled with rosuvastatin, perindopril and indapamide given concurrently at the same dose level as in the combination for treatment of essential hypertension and one of the following coincident conditions: primary hypercholesterolemia (type IIa including heterozygous familial hypercholesterolemia), mixed dyslipidaemia (type IIb) or homozygous familial hypercholesterolemia.

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

II. QUALITY ASPECTS

II.1 Introduction

The chemical-pharmaceutical assessment report concerns the application of Roxiper 10 mg/4 mg/1.25 mg, 20 mg/4 mg/1.25 mg, 10 mg/8 mg/2.5 mg and 20 mg/8 mg/2.5 mg film-coated tablets (rosuvastatin/perindopril/indapamide) via a decentralized procedure according to Article 10.b of Directive 2001/83/(i.e. a fixed dose combination application). The products have been developed by Krka, d.d., Novo mesto.

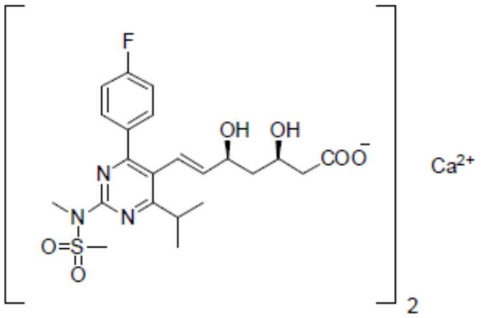
For the bioequivalence study, reference products are Bionoliprel® film-coated tablets (perindopril arginine and indapamide) and Crestor® tablets (rosuvastatin), original products of Les Laboratories Servier and AstraZeneca, respectively.

II.2 Drug substances

II.2.1 Rosuvastatin calcium

Data on the quality and manufacture of the rosuvastatin calcium active substance were provided in the submission using the Active Substance Master File (ASMF) procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

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



The active 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 as well as X-ray powder diffraction. The impurity profile of the drug substance contains detailed information about genotoxic impurities, residual solvents and catalysts.

Rosuvastatin calcium has a valid European Pharmacopoeia (Ph. Eur.) monograph. The substance is specified according to the requirements of the current Ph. Eur. monograph, additional specification has been set for residual solvents, heavy metals, particle size, polymorphic form and microbiological purity. The Ph. Eur. specification includes the following tests: appearance, solubility, identification (IR, enantiomeric purity and calcium), water content, related substances, assay and enantiomeric purity.

Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the active 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.

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.

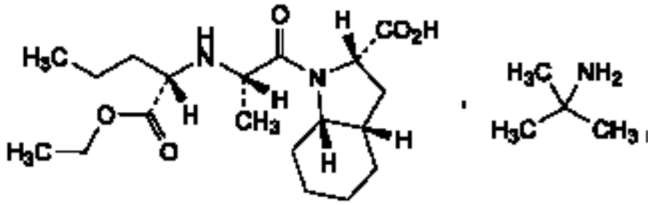
Good Manufacturing Practice (GMP) compliance of the drug substance manufacture is demonstrated by the applicant.

II.2.2 Perindopril tert-butylamine

Data on the quality and manufacture of the drug substance (perindopril tert-butylamine, perindopril erbumine) were provided in the submission using the ASMF procedure with additional data in the marketing authorization dossier. 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-oxopentan-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, FT-IR and XRPD spectroscopy. The impurity profile of the substance contains detailed information about genotoxic impurities, residual solvents and catalysts.

The drug substance is specified according to the requirements of the current Ph. Eur. monograph, additional specification has only been set for residual solvents. 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).

Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the active 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.

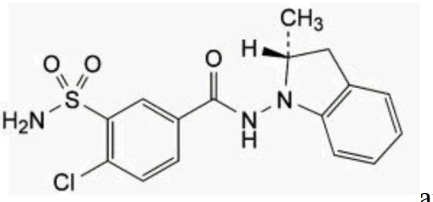
Stability studies have been performed with the drug substance. According to the presented stability data the proposed re-test period is acceptable if stored below 25 °C in the original packaging material in order to protect from moisture.

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

II.2.3 Indapamide

Data on the quality and manufacture of the drug substance were provided in the submission using the Ph. Eur. Certificate of Suitability (CEP) procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: indapamide
Chemical name: 4-chloro-N-[(2RS)-2-methyl-2,3-dihydro-1H-indol-1-yl]-3 sulphamoylbenzamide
Structure:



and enantiomer

The drug substance is a white or almost white powder and is practically insoluble in water, soluble in ethanol (96%).

The substance is specified according to the requirements of the current Ph. Eur. monograph, additional specifications have only been set for residual solvents and particle size. The Ph. Eur. specification includes the following tests for indapamide: appearance, solubility, identification (IR, UV spectrophotometry, TLC), optical rotation, related substances (HPLC), impurity A (HPLC), impurity C (TLC), water content, sulphated ash and assay (HPLC).

Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the active 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.

A retest period and the packaging material (double polyethylene bag inside a fibre drum) have been mentioned on the CEPs.

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 fixed dose combination product with rosuvastatin, perindopril erbumine and indapamide into a single tablet to support patient adherence that was bioequivalent to the reference products Bionoliprel (perindopril arginine/indapamide) 5 mg/1.25 mg and 10 mg/2.5 mg film-coated tablets (Servier) and Crestor (rosuvastatin) 10 mg and 20 mg 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 products with the following appearance and composition was obtained.

> 10 mg/4 mg/1.25 mg strength: reddish-brown, round, slightly biconvex film-coated tablets with bevelled edges, engraved with mark PIR1 on one side of the tablet. Diameter: approx. 7.5 mm.
>
> 20 mg/4 mg/1.25 mg strength: **o**ff-pink, round, slightly biconvex film-coated tablets with bevelled edges, engraved with mark PIR2 on one side of the tablet. Diameter: approx. 10 mm.
>
> 10 mg/8 mg/2.5 mg strength: **l**ight pink, round, slightly biconvex film-coated tablets with bevelled edges, engraved with mark PIR3 on one side of the tablet. Diameter: approx. 10 mm.
>
> 20 mg/8 mg/2.5 mg strength: **p**ale pinkish-brown, round, slightly biconvex film-coated tablets with bevelled edges, engraved with mark PIR4 on one side of the tablet. Diameter: approx. 10 mm.

The excipients used in the finished product are microcrystalline cellulose (type 200 LM and type 112), crospovidone (type A), colloidal anhydrous silica, magnesium stearate and film-coating (poly(vinyl alcohol), titanium dioxide (E171), macrogol 3350, talc and red/yellow/black iron oxide (E172)).

All excipients used comply with their respective Ph. Eur. monographs. 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 International Council of Harmonisation (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 24 months is approved when stored 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 products have been shown to meet the current regulatory requirements with regards to their 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 quality aspects the products are approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of rosuvastatin, perindopril and indapamide are well known. No further studies non-clinical are required. Overview based on literature review is appropriate.

III.2 Pharmacology

Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, perindopril tert-butylamine salt is an angiotensin-converting enzyme inhibitor, and indapamide is a chlorosulfamoyl diuretic, The pharmacological properties of this combination are derived from those of each of the components taken separately, in addition to those due to the additive synergic action of perindopril and indapamide when combined.

III.3 Pharmacokinetics

Rosuvastatin

Absorption: maximum rosuvastatin plasma concentrations are achieved a few hours after oral administration. Distribution: 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. Biotransformation: 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. Elimination: rosuvastatin is excreted mainly unchanged in the faeces (consisting of absorbed and non-absorbed active substance) and the remaining part is excreted in urine. The elimination half-life does not increase at higher doses. Linearity/non-linearity: systemic exposure of rosuvastatin increases in proportion to dose. There are no changes in pharmacokinetic parameters following multiple daily doses.

Perindopril

Absorption: after oral administration, the absorption of perindopril is rapid. Biotransformation: perindopril is a prodrug, the active metabolite is perindoprilat. In addition to active perindoprilat, perindopril yields five metabolites, all inactive. Ingestion of food decreases conversion to perindoprilat, hence bioavailability. Perindoprilat is eliminated in the urine. Linearity/non-linearity: it has been demonstrated a linear relationship between the dose of perindopril and its

plasma exposure.

Indapamide

Absorption: indapamide is rapidly and completely absorbed from the digestive tract. Elimination is mainly in the urine and faeces in the form of active metabolites.

III.4 Toxicology

Preclinical data on *rosuvastatin* reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenicity potential. Specific tests for effects on hERG have not been evaluated. Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels were as follows: 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, with reduced litter sizes, litter weight and pup survival observed at maternally toxic doses, where systemic exposures were several times above the therapeutic exposure level.

Perindopril/indapamide combination has slightly increased toxicity than that of its components. Renal manifestations do not seem to be potentiated in the rat. However, the combination produces gastro-intestinal toxicity in the dog and the toxic effects on the mother seem to be increased in the rat (compared to perindopril). Nonetheless, these adverse effects are shown at dose levels corresponding to a very marked safety margin by comparison to the therapeutic doses used.

Preclinical studies performed separately with perindopril and indapamide did not show genotoxic, carcinogenic or teratogenic potential.

III.5 Ecotoxicology/environmental risk assessment (ERA)

The combination product is intended for substitution indication and as such will replace use of the co-administered perindopril, indapamide and rosuvastatin. Thus the exposure of the environment to the active substances will not increase by use of this product. An environmental risk assessment therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

The literature review describing the non-clinical data of the three active principles of the combination is adequate. From non-clinical aspects the products are 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 and a pharmacokinetic interaction study. Such studies are sufficient for this type of application.

IV.2 Pharmacokinetics

IV.2.1 Literature data

The applicant submitted a literature overview on the known pharmacokinetic characteristics of the active principles of this combination product.

Rosuvastatin

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. The volume of distribution of rosuvastatin is approximately 134 L. Approximately 90% of rosuvastatin is bound to plasma proteins, mainly to albumin.

Rosuvastatin undergoes limited metabolism (approximately 10%). 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 accounts for greater than 90% of the circulating HMGCoA reductase inhibitor activity.

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. Approximately 5% is excreted unchanged in urine. The plasma elimination half-life is approximately 20 hours. The elimination half-life does not increase at higher doses. The geometric mean plasma clearance is approximately 50 litres/hour (coefficient of variation 21.7%). As with other HMG-CoA reductase inhibitors, the hepatic uptake of rosuvastatin involves the membrane transporter OATP-C. This transporter is important in the hepatic elimination of rosuvastatin.

Linearity/non-linearity: systemic exposure of rosuvastatin increases in proportion to

dose. There are no changes in pharmacokinetic parameters following multiple daily doses.

Perindopril

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.

The volume of distribution is approximately 0.2 l/kg for unbound perindoprilat. Protein binding of perindoprilat to plasma proteins is 20%, principally to angiotensin converting enzyme, but is concentration-dependent.

Twenty seven percent of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours. 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.

It has been demonstrated a linear relationship between the dose of perindopril and its plasma exposure.

Indapamide

Indapamide is rapidly and completely absorbed from the digestive tract. The peak plasma level is reached in humans approximately one hour after oral administration of the product. Plasma protein binding is 79%.

The elimination half-life is between 14 and 24 hours (average 18 hours). Repeated administration does not produce accumulation. Elimination is mainly in the urine (70% of the dose) and faeces (22%) in the form of inactive metabolites.

IV.2.2 Pharmacokinetic interaction study

The applicant performed a pharmacokinetic interaction study between rosuvastatin and perindopril/indapamide. No relevant changes were noted in plasma concentrations or pharmacokinetic parameters of rosuvastatin, perindopril, perindoprilat and indapamide when rosuvastatin, perindopril and indapamide were given concomitantly and no significant pharmacokinetic interaction effect was observed. Also based on comprehensive literature review it was concluded that no clinically significant pharmacokinetic interaction between the three drug substances is expected, which is in accordance with *in vivo* study results.

IV.2.2 Bioequivalence studies

Three pivotal bioequivalence studies have been conducted according to the bioequivalence guideline in force (CPMP/EWP/QWP/1401/98/ Rev 1/Corr** 2010).

The 20 mg/8 mg/2.5 fixed combination

A single-dose, randomized, open-label, laboratory blind, crossover, two-period, two-treatment, two-sequence, bioequivalence study between rosuvastatin/perindopril/indapamide/ 20 mg/8 mg/2.5 mg/ fixed combination film-coated tablets (Krka d.d., Novo mesto, Slovenia) (Test) and the co-administered Bionoliprel® 10 mg/2.5 mg (perindopril arginine/indapamide) film-coated tablets Servier (Ireland) Industries Ltd., Ireland, EU) (Reference 1) and Crestor® 20 mg (rosuvastatin) film-coated tablets (AstraZeneca UK Ltd, UK and Corden Pharma GmbH, Germany) (Reference 2) in healthy adult subjects under fasting conditions.

Results for rosuvastatin:

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%[1]
$AUC_{(0-t)}$ (pg*h/mL)	106.49	100.36 - 112.99	18
Cmax (pg/mL)	105.46	98.00 - 113.49	22

[1] Estimated from the Residual Mean Squares.

Results for perindopril:

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%[1]
$AUC_{(0-t)}$ (ng*h/mL)	96.81	94.07 - 99.64	9
Cmax (ng/mL)	99.34	93.88 - 105.12	17

Results for indapamide:

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%[1]
$AUC_{(0-t)}$ (ng*h/mL)	103.93	101.98 - 105.91	6
Cmax (ng/mL)	103.95	100.56 - 107.46	10

The 90% confidence intervals of the relative mean indapamide, rosuvastatin and perindopril AUC_t and C_{max} of the Test to Reference products were within the 80.00 – 125.00% range.

The above results support that a single dose of Test product is bioequivalent with single doses of the co-administered two Reference products (Reference 1 and Reference 2) in healthy adult subjects under fasting condition.

The 10 mg/8 mg/2.5 mg fixed combination

A single-dose, randomized, open-label, laboratory blind, crossover, two-period, two-treatment, two-sequence, bioequivalence study between rosuvastatin/perindopril/indapamide/ 10 mg/8 mg/2.5 mg/ fixed combination film-coated tablets (Krka d.d., Novo mesto, Slovenia) (Test) and the co-administered Bionoliprel® 10 mg/2.5 mg (perindopril arginine/indapamide) film-coated tablets (Servier Pharma d.o.o., Slovenia, EU) (Reference 1) and Crestor® 10 mg (rosuvastatin) film-coated tablets (AstraZeneca GmbH, Germany, EU) (Reference 2) in healthy adult subjects under fasting conditions.

Results for rosuvastatin:

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%[1]
$AUC_{(0-t)}$ (pg*h/mL)	95.15	89.93 - 100.68	17.1
Cmax (pg/mL)	97.06	90.86 - 103.68	20.1

[1] Estimated from the Residual Mean Squares.

Results for perindopril:

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%[1]
$AUC_{(0-t)}$ (ng*h/mL)	95.55	92.64 - 98.56	9.3
Cmax (ng/mL)	99.94	94.23 - 106.00	17.9

Results for indapamide:

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%[1]
$AUC_{(0-t)}$ (ng*h/mL)	105.28	103.17 - 107.43	6.1
Cmax (ng/mL)	104.34	100.03 - 108.84	12.8

The 90% confidence intervals of the relative mean indapamide, rosuvastatin and perindopril AUC_{0-t} and C_{max} of the Test to Reference products were within the 80.00 – 125.00% range.

The above results support that a single dose of Test product is bioequivalent with single doses of the co-administered two Reference products (Reference 1 and Reference 2) in healthy adult subjects under fasting condition.

The 20 mg/4 mg/1.25 mg fixed combination

A single-dose, randomized, open-label, laboratory blind, crossover, two-period, two-treatment, two-sequence, bioequivalence study between rosuvastatin/perindopril/indapamide/ 20 mg/4 mg/1.25 mg fixed combination film-coated tablets (Krka d.d., Novo mesto, Slovenia) (Test) and the co-administered Bionoliprel® 5 mg/1.25 mg (perindopril arginine/indapamide) film-coated tablets (Servier Pharma d.o.o., Slovenia, EU) (Reference 1) and Crestor® 20 mg (rosuvastatin) film-coated tablets (AstraZeneca UK Ltd, UK, EU) (Reference 2) in healthy adult subjects under fasting conditions.
Results for rosuvastatin:

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%[1]
$AUC_{(0-t)}$ (pg*h/mL)	96.69	91.93 - 101.70	15
Cmax (pg/mL)	97.99	91.80 - 104.60	20

[1] Estimated from the Residual Mean Squares.

Results for perindopril:

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%[1]
$AUC_{(0-t)}$ (ng*h/mL)	97.96	95.49 - 100.49	8
Cmax (ng/mL)	103.02	98.10 - 108.20	15

Results for indapamide:

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%[1]
$AUC_{(0-t)}$ (ng*h/mL)	102.26	100.50 - 104.05	5
Cmax (ng/mL)	107.24	104.47 - 110.09	8

The 90% confidence intervals of the relative mean indapamide, rosuvastatin and perindopril AUC_{0-t} and C_{max} of the Test to Reference products were within the 80.00 – 125.00% range.

The above results support that a single dose of Test product is bioequivalent with single doses of the co-administered two Reference products (Reference 1 and Reference 2) in healthy adult subjects, under fasting condition.

Biowaiver

The applicant claimed for biowaiver for the dose strength of 10 mg/4 mg/1.25 mg fixed combination on the basis of general biowaiver requirements described in the guideline CPMP/EWP/QWP/1401/98 Rev 1 Corr**. The biowaiver can be granted.

IV.3 Pharmacodynamics

Rosuvastatin, perindopril and indapamide 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 discussed the rationale for the combination and the recommendations of therapeutic guidelines.

Efficacy of the monocomponents were summarized, furthermore the applicant provided publications on efficacy of the combination as well.

Co-prescription data from several EU countries were submitted demonstrating the clinical use of the combination in the proposed dose strengths.

Additionally as supportive data the applicant submitted a post-hoc analysis of own non-interventional efficacy and safety study with rosuvastatin in patients with hyperlipidaemia, in a group of patients who took perindopril and indapamide concomitantly.

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 publications with the combination of the active substances as well to support the safety of this fixed dose combination. Safety data from the bioequivalence studies and from Krka's post-hoc analysis of own non-interventional study were also presented.

The applicant provided a safety analysis of data from WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden.

Safety data have shown that the concomitant perindopril, indapamide and rosuvastatin would not expose patient to any new or unexpected adverse events.

The submitted data are acceptable and the totality of evidence justifies positive benefit-risk ratio of the fixed dose combination.

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 new legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant Good Vigilance Practice module, the Summary is considered acceptable.

IV.6.2 Risk Management Plan

Summary of safety concerns

Important identified risks	Skeletal muscle effects: rhabdomyolysis, myopathy, myositis, myalgia, creatine kinase increases, myoglobinaemia, and myoglobinuria
	Dual blockade of renin-angiotensin-aldosterone system (RAAS)
	Renal impairment (including renal failure)
	Hepatic effects: permanently increased transaminases, hepatitis, jaundice, hepatic encephalopathia, hepatic impairment
	Hypersensitivity reactions (including angioedema, intestinal angioedema, concomitant use of mTOR inhibitor, photosensitivity and anaphylactoid reactions)
	Electrolyte abnormalities including hypo- and hyperkalaemia
	Neutropenia/agranulocytosis
	Stevens-Johnson syndrome and Toxic epidermal necrolysis
	Use during pregnancy and lactation
	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.
Important potential risks	Interstitial lung disease
	Off label use
Missing information	Use in paediatric population
	Use in patients undergoing dialysis
	Use in patients with untreated decompensated heart failure
	Long-term safety of the combination

Pharmacovigilance Plan: routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to Krka's products containing rosuvastatin/perindopril/indapamide. No additional activities are proposed.

Risk Minimisation Measures: routine measures (i.e. wording in the Summary of Product Characteristics, package leaflet and classification as a prescription-only medicine) are considered sufficient to manage all of the safety concerns connected to Krka's products containing rosuvastatin/perindopril/indapamide. No additional activities are proposed. For any further information on risk minimisation refer to the product information.

IV.6.3 Periodic Safety Update Reports

The holder of the marketing authorisation shall submit the first periodic safety update report for this product with a period of 5 years following authorisation. Further, the marketing authorisation holder(s) 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 animals and humans. For these application the bioequivalence studies described in section IV.2 are pivotal.

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

The applicant demonstrated bioequivalence between the combination and co-administered monocomponent reference products. A pharmacokinetic interaction study between rosuvastatin and perindopril/indapamide was also performed.

Overall, the provided clinical overview is considered sufficient to justify the rationale of this particular combination when used to substitute patients already on stable doses of the separate agents.

From clinical aspects the products are approvable.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present applications concern Roxiper 10 mg/4 mg/1.25 mg, 20 mg/4 mg/1.25 mg, 10 mg/8 mg/2.5 mg and 20 mg/8 mg/2.5 mg coated tablets, fixed dose combinations of rosuvastatin/perindopril tert-butylamine/indapamide. The applicant and the future holder of authorisation is Krka d.d., Slovenia.

The products are indicated for substitution therapy in adult patients adequately controlled with rosuvastatin, perindopril and indapamide given concurrently at the same dose level as in the combination for treatment of essential hypertension and one of the following coincident conditions: primary hypercholesterolemia (type IIa including heterozygous familial hypercholesterolemia), mixed dyslipidaemia (type IIb) or homozygous familial hypercholesterolemia.

The application for these combination products contains an adequate review of published non-clinical and clinical data. The applicant demonstrated bioequivalence between the combination and co-administered monocomponent reference products. A pharmacokinetic interaction study between rosuvastatin and perindopril/indapamide was also performed.

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 marketing authorisation for Roxiper 10 mg/4 mg/1.25 mg, 20 mg/4 mg/1.25 mg, 10 mg/8 mg/2.5 mg and 20 mg/8 mg/2.5 mg coated tablets.

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

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
Type IB B.II.f.1.b.1 Extension of the shelf-life of the medicinal product as packed for sale from 24 to 36 months	HU/H/0484/ 001-004/ IB/01	no	28 September 2018	28 October 2018	approval	no