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Public Assessment Report

Name of the Product:

Ravalsyo

10 mg/80 mg, 20 mg/80 mg,
10 mg/160 mg, 20 mg/160 mg film-coated tablets

(rosuvastatin/valsartan)

Procedure number: HU/H/0421/001-004/DC

Marketing authorisation holder: Krka d.d.

Date: 6 January 2017

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Ravalsyo (in Bulgaria Valsaros, in Estonia and Latvia Valarox, in the Slovak Republic Ravalsya) 10 mg/80 mg, 20 mg/80 mg, 10 mg/160 mg, 20 mg/160 mg film-coated tablets. The holder of the marketing authorisation is Krka d.d.

The active substances are valsartan and rosuvastatin. Each film-coated tablet contains 10 mg or 20 mg rosuvastatin (as calcium) and 80 mg or 160 mg valsartan, respectively.

The other ingredients are
- tablet core: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate, mannitol, povidone K25, sodium laurilsulfate and yellow iron oxide (E172);
- film-coating: poly(vinyl alcohol), titanium dioxide (E171), macrogol 3000, talc, red iron oxide (E172, only for 10 mg/80 mg, 20 mg/80 mg and 10 mg/160 mg film-coated tablets) and yellow iron oxide (E172, only for 10 mg/160 mg and 20 mg/160 mg film-coated tablets).

The 10 mg/80 mg film-coated tablets are dark pink, round, slightly biconvex, with bevelled edges, engraved with a mark K4 on one side of the tablet. Tablet diameter: 8.7–9.3 mm.

The 20 mg/80 mg film-coated tablets are dark pink, capsule-shaped, slightly biconvex, engraved with a mark K3 on one side of the tablet. Tablet dimensions: 14.7–15.3 mm x 6.7–7.3 mm.

The 10 mg/160 mg film-coated tablets are dark pink, oval, biconvex, engraved with a mark K2 on one side of the tablet. Tablet dimensions: 16.7–17.3 mm x 7.7–8.3 mm.

The 20 mg/160 mg film-coated tablets are light brownish-yellow, oval, biconvex, engraved with a mark K1 on one side of the tablet. Tablet dimensions: 16.7–17.3 mm x 7.7–8.3 mm.

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

Ravalsyo is indicated for treatment of increased blood pressure and concomitant high cholesterol level and/or for prevention of cardiovascular events.

What patients need to know before taking Ravalsyo?

Those who
- are allergic to valsartan, rosuvastatin or any of the other ingredients of this medicine;
- are pregnant or breast-feeding. If a patient becomes pregnant while taking Ravalsyo, she must stop taking it immediately and consult the doctor. Women should avoid becoming

pregnant while taking Ravalsyo by using suitable contraception;
- have liver disease;
- have severe kidney problems;
- have repeated or unexplained muscle aches or pains;
- take a drug called ciclosporin (used, for example, after organ transplants);
- have diabetes or impaired kidney function and are treated with a blood pressure lowering medicine containing aliskiren;

must not take Ravalsyo, they must consult their doctor, even when they are in doubt whether any of the above mentioned applies.

Warnings and precautions

Those who
- have problems with the kidneys or if are undergoing dialysis;
- have problems with the liver;
- 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. The doctor must be informed immediately if unexplained muscle aches or pains are experienced especially if feeling also unwell or having a fever;
- regularly drink large amounts of alcohol;
- have thyroid gland that is not working properly;
- take other medicines called fibrates to lower the cholesterol;
- take medicines used to fight the HIV infection e.g. ritonavir with lopinavir and/or atazanavir (see "Other medicines and Ravalsyo");
- are over 70 (as the doctor needs to choose the right start dose of Ravalsyo to suit the patient);
- have severe respiratory failure;
- are of Asian origin – that is Japanese, Chinese, Filipino, Vietnamese, Korean and Indian. The doctor needs to choose the right start dose of Ravalsyo to suit the patient;
- are suffering from a narrowing of the kidney artery;
- have recently undergone kidney transplantation (received a new kidney);
- are treated after a heart attack or for heart failure, the doctor may check the kidney function;
- have severe heart disease other than heart failure or heart attack;
- have ever experienced swelling of the tongue and face caused by an allergic reaction called angioedema when taking another drug (including ACE inhibitors). The doctor must be informed accordingly. If these symptoms occur when taking Ravalsyo, its taking must be stopped immediately and it must never be taken again. (See also the section "Possible side effects");
- taking medicines that increase the amount of potassium in the blood. These include potassium supplements or salt substitutes containing potassium, potassium-sparing medicines and heparin. It may be necessary to check the amount of potassium in the blood at regular intervals;
- suffer from aldosteronism. This is a disease in which the adrenal glands make too much of the hormone aldosterone. If this applies to you, the use of <Invented name> is not recommended.

- have lost a lot of fluid (dehydration) caused by diarrhoea, vomiting, or high doses of water pills (diuretics).
- are taking any of the following medicines used to treat high blood pressure:
  - an ACE-inhibitor (for example enalapril, lisinopril, ramipril), in particular if having diabetes-related kidney problems.
  - aliskiren;
- are being treated with an ACE-inhibitor together with certain other medicines to treat heart failure, which are known as mineralocorticoid receptors antagonists (MRA, for example spironolactone, eplerenone) or betablockers (for example metoprolol);
- 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 Ravalsyo can lead to serious muscle problems: rhabdomyolysis)

must consult their doctor before taking Ravalsyo.

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 Ravalsyo.

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

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

Other medicines and Ravalsyo

Patients should inform their doctor if taking, or have recently taken any other medicines, including any bought without a prescription. The doctor must particularly be informed if the patient takes any of the following:

- ciclosporin (used for example, after organ transplants);
- warfarin (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);
- erythromycin (an antibiotic);
- an oral contraceptive (the pill);
- hormone replacement therapy;
- other medicines that lower blood pressure, especially water pills (diuretics);
- medicines that increase the amount of potassium in the blood. These include potassium supplements or salt substitutes containing potassium, potassium-sparing medicines and heparin;
- certain type of pain killers called non-steroidal anti-inflammatory medicines (NSAIDs);
- some antibiotics (rifamycin group) or an antiretroviral drug used to treat HIV/AIDS infection (ritonavir with lopinavir and/or atazanavir). These drugs may increase the effect of Ravalsyo;

- lithium, a medicine used to treat some types of psychiatric illness;
- taking an ACE-inhibitor or aliskiren (see also information under the headings "Do not take Ravalsyo" and "Warnings and precautions");
- the patient is being treated with an ACE-inhibitor together with certain other medicines to treat the heart failure, which are known as mineralocorticoid receptors antagonists (MRA, for example spironolactone, eplerenone) or betablockers (for example metoprolol);
- taking oral fusidic acid to treat a bacterial infection the patient will need to temporarily stop using this medicine. The doctor will advise when it is safe to restart Ravalsyo. Taking Ravalsyo with fusidic acid may rarely lead to muscle weakness, tenderness or pain (rhabdomyolysis).

The effects of the above medicines could be changed by Ravalsyo or they could change the effects of Ravalsyo.

Ravalsyo with food and drink

Ravalsyo can be taken with or without food.

Pregnancy and breast-feeding

Those who are pregnant or breast-feeding must not take Ravalsyo. If becoming pregnant while taking Ravalsyo its use must be stopped immediately and the doctor consulted. Women should avoid becoming pregnant while taking Ravalsyo by using suitable contraception.

Patients must tell their doctor if they think that they are (or might become) pregnant. The doctor will normally advise them to stop taking Ravalsyo before becoming pregnant or as soon as they know they are pregnant, and will advise them to take another medicine instead of Ravalsyo.

Patients must tell your doctor if they are breast-feeding or about to start breast-feeding. Ravalsyo is not recommended for mothers who are breast-feeding, and the doctor may choose another treatment for them if wishing to breast-feed.

Driving and using machines

Before driving a vehicle, using tools or operating machines, or carry out other activities that require concentration, patients make sure they know how Ravalsyo affects them. Like many other medicines used to treat high blood pressure, Ravalsyo may, in rare cases, cause dizziness and affect the ability to concentrate. If the patient feels dizzy, the doctor should be consulted before attempting to drive or use machines.

Ravalsyo contains lactose

Those who have been told by their doctor that they have an intolerance to some sugars, contact their doctor before taking this medicinal product.

How to take Ravalsyo?

Usual doses in adults: the recommended dose is one tablet per day.

This medicine can be used before or after food and drinks. Patients should take this medicine at the same time each day with a drink of water. They should not take Ravalsyo with grapefruit juice.

Use in children and adolescents: Ravalsyo should not be used in children and adolescents.

Regular cholesterol checks

It is important to go back to the doctor for regular cholesterol checks, to make sure the cholesterol has reached and is staying at the correct level. The doctor may decide to increase the dose so that the patient is are taking the amount of Ravalsyo that is right for him/her.

What to do if you take more Ravalsyo has been taken than it should have been?

The doctor or a nearest hospital must be contacted for advice. If experiencing severe dizziness and/or fainting, the patient should lay down. If going into hospital or receive treatment for another condition, the medical staff should be informed on taking Ravalsyo.

What to do if taking Ravalsyo was forgotten?

The patient should not worry, he/she just should take the next scheduled dose at the correct time. A double dose to make up for a forgotten tablet should never be taken.

May taking Ravalsyo be stopped by the patient?

Patients are advised to talk to their doctor if they want to stop taking Ravalsyo. Stopping this treatment may cause the disease to get worse. The cholesterol levels might increase again if stopping taking Ravalsyo. Thus, patients should not stop taking this medicine unless the doctor tells to do so.

Possible side effects

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

It is important that patients are aware of what these side effects may be. They are usually mild and disappear after a short time.

Patients must stop taking Ravalsyo and seek medical help immediately if experiencing any of the following side effects:
- 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 itching of the skin (with raised lumps);
- blistering of the skin, mouth, eyes and/or genitals (Stevens-Johnson syndrome).

Also, patients must stop taking Ravalsyo and talk to their doctor immediately if experiencing any unusual aches or pains in the muscles which go on for longer than it might 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*.

The other side effects are as follows.

Common **(**that may affect up to 1 in 10 people):
- dizziness,
- low blood pressure with or without symptoms such as dizziness and fainting when standing up,
- decreased kidney function (signs of renal impairment),
- headache,
- abdominal pain,
- constipation,
- feeling sick (nausea),
- muscle pain,
- feeling weak,
- diabetes. This is more likely if the patient has 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.

Uncommon (that may affect up to 1 in 100 people):
- angioedema,
- sudden loss of consciousness (syncope),
- spinning sensation (vertigo),
- severely decreased kidney function (signs of acute renal failure),
- muscle spasms, abnormal heart rhythm (signs of hyperkalaemia),
- breathlessness, difficulty breathing when lying down, swelling of the feet or legs (signs of cardiac failure),
- cough,
- diarrhoea,
- tiredness,
- weakness,
- rash, itching or other skin reactions,
- an increase in the amount of protein in the urine – this usually returns to normal on its own without having to stop taking Ravalsyo tablets.

Rare (that may affect up to 1 in 1,000 people):
- 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, must stop taking Ravalsyo and seek medical help immediately,
- muscle damage in adults – as a precaution, who experiences any unusual aches or pains in the muscles which go on for longer than expected should stop taking Ravalsyo and talk to the doctor immediately,
- a severe stomach pain (inflamed pancreas),
- increase in liver enzymes in the blood,
- reduction in blood platelets, which increases risk of bleeding or bruising (thrombocytopenia).

Very rare (that may affect up to 1 in 10,000 people):
- jaundice (yellowing of the skin and eyes),
- hepatitis (an inflamed liver),
- traces of blood in the urine,
- damage to the nerves of the legs and arms (such as numbness),
- joint pain,
- memory loss,
- gynecomastia (breast enlargement in men).

Not known (i.e. its frequency cannot be estimated from the available data):
- allergic reactions with rash, itching and hives; symptoms of fever, swollen joints and joint pain, muscle pain, swollen lymph nodes and/or flu-like symptoms may occur (signs of serum sickness),
- purplish-red spots, fever, itching (signs of inflammation of blood vessels also called vasculitis),
- fever, sore throat or mouth ulcers due to infections (symptoms of low level of white blood cells also called neutropenia),
- decrease of level of haemoglobin and decrease of the percentage of red blood cells in the blood (which lead to anaemia in severe cases),
- increase of level of potassium in the blood (which can trigger muscle spasms, abnormal heart rhythm in severe cases),
- decreased level of sodium in the blood (which can cause tiredness and confusion, muscle twitching, fits or coma),
- elevation of liver function values (which can indicate liver damage) including an increase of bilirubin in the blood (which can trigger yellow skin and eyes in severe cases),
- increase of level of blood urea nitrogen and increase of level of serum creatinine (which can indicate abnormal kidney function),
- Stevens-Johnson syndrome (serious blistering condition of the skin, mouth, eyes and genitals),
- shortness of breath,
- oedema (swelling),
- sleep disturbances, including insomnia and nightmares,
- sexual difficulties,
- depression,
- breathing problems, including persistent cough and/or shortness of breath or fever,

- tendon injury,
- muscle weakness that is constant.

The frequency of some side effects may vary depending on the patient's condition. For example, side effects such as dizziness, and decreased kidney function were seen less frequently in patients treated with high blood pressure than in patients treated for heart failure or after a recent heart attack.

How to store Ravalsyo?

It should be stored in the original package in order to protect from moisture.

This medicine must be 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 Ravalsyo (in Bulgaria Valsaros, in Estonia and Latvia Valarox, in the Slovak Republic Ravalsya) 10 mg/80 mg, 20 mg/80 mg, 10 mg/160 mg, 20 mg/160 mg film-coated tablets. The procedure was finalised at 29 August 2016. 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: Austria, Bulgaria, the Czech Republic, Estonia, Finland, Latvia, Lithuania, Poland, Portugal, Romania, the Slovak Republic, Slovenia, Spain) concerned fix dose combinations of rosuvastatin/valsartan 10 mg/80 mg, 20 mg/80 mg, 10 mg/160 mg, 20 mg/160 mg film-coated tablets.

The application has been filed pursuant to Article 10b of Directive 2001/83/EC (so called "fix dose combination application"). Its basis was the lack of marketing authorization of any rosuvastatin/valsartan combination in the European Union. The applicant applied for a marketing authorisation of the product with different strengths for substitution therapy of hypertension in patients with high risk of cardiovascular events and/or primary hypercholesterolemia already receiving the same active ingredients as monocomponents in the respective doses. The application contained no new clinical or preclinical data, other than two bioequivalence studies with Diovan (valsartan, Novartis) and Crestor (rosuvastatin, AstraZeneca) film-coated tablets, the supporting literature where necessary and, in addition, co-prescription data from representative EU member states.

Considering the substitution indication the reference products were Diovan 80 mg/160 mg film-coated tablets by Novartis and Crestor 10 mg/20 mg film-coated tablet by AstraZeneca, authorised for marketing since 1996 and 2003, respectively.

The products are indicated for the following conditions: as substitution therapy for those patients who are adequately controlled with rosuvastatin and valsartan given concurrently, at the same dose level as in the combination for the treatment of hypertension in adult patients who are estimated to have a high risk for a first cardiovascular event (for prevention of major cardiovascular events) or with one of the following coincident conditions:

- primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIb),
- homozygous familial hypercholesterolaemia.

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

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisations for Ravalsyo (in Bulgaria Valsaros, in Estonia and Latvia Valarox, in the Slovak Republic Ravalsya) 10 mg/80 mg, 20 mg/80 mg, 10 mg/160 mg and 20 mg/160 mg film-coated tablets from Krka d.d. Novo mesto, Slovenia.

II. QUALITY ASPECTS

II.1 Introduction

This chemical-pharmaceutical assessment report concerns the application for marketing authorisation via the Decentralised Procedure for products rosuvastatin/valsartan 10 mg/80 mg, 20 mg/80 mg, 10 mg/160 mg and 20 mg/160 mg film-coated tablets, according to Article 10b of the consolidated Directive 2001/83/EC (i.e. a fixed combination application). The products have been developed by Krka, Slovenia.

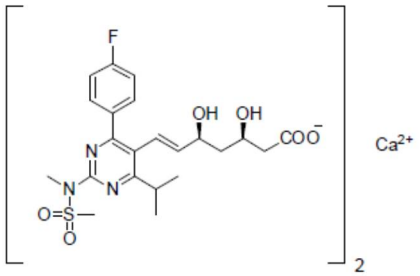
For the bioequivalence studies the reference products have been Crestor® containing rosuvastatin (AstraZeneca) and Diovan® containing valsartan (Novartis).

II.2 Drug substances

II.2.1 Rosuvastatin calcium

Data on the quality and manufacture of the 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
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:



Rosuvastatin calcium is slightly soluble in water, freely soluble in methylene chloride and practically insoluble in anhydrous ethanol according to the European Pharmacopoeia (Ph. Eur.). Solubility of rosuvastatin calcium in various buffered aqueous media was also determined. Solubility in pH 6.8 phosphate buffer and in pH 4.5 acetate buffer is more than 0.2 mg/ml. Its amorphous form has been confirmed. Rosuvastatin calcium contains three isomeric centres, the active substance is the (E,3*R*,5*S*) isomer.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the drug substance (active pharmaceutical ingredient, API) is adequate.

Evidence of the structure has been confirmed by ^{1}H-NMR, ^{13}C-NMR, MS, FT-IR, and XRPD. The impurity profile of the API contains detailed information about genotoxic impurities, residual solvents and catalysts.

Rosuvastatin calcium has a valid Ph. Eur. monograph. The specification set by the drug product manufacturer includes parameters prescribed in the monograph, supplemented by additional in-house test: appearance, identification of rosuvastatin by IR and enantiomeric purity, identification of calcium, water content (Karl Fischer), related substances, assay, enantiomeric purity, residual solvents, heavy metals, particle size, polymorphic form and microbiological purity. The specification of rosuvastatin calcium is adequate to control the active substance.

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 drug 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.

The drug substance is packed under nitrogen in a primary bag made of polyethylene low density foil, and a secondary bag made of laminated PET/Al/PE foil.

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.

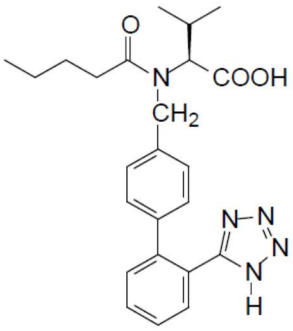
Good Manufacturing Practice (GMP) compliance of the API manufacture is demonstrated by the applicant.

II.2.2 Valsartan

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

INN name: valsartan
Chemical name: (2*S*)-3-Methyl-2-[pentanoyl[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]-methyl]amino] butanoic acid

Structure:



The drug substance is white to almost white hygroscopic powder, freely soluble in anhydrous ethanol, sparingly soluble in dichloromethane, practically insoluble in water. The molecule has one chiral centre, the manufacturer consistently produces the correct isomer (2*S*). Valsartan exists in amorphous form. No other polymorphic forms are known, except some solvates. The manufacturer consistently produces the amorphous form.

Valsartan is specified by the drug product manufacturer according to the requirements of the current Ph. Eur. monograph, which includes the following tests: appearance, solubility, identification, specific optical rotation, enantiomeric purity, chromatographic purity, heavy metals, water content, sulphated ash and assay. Additional specifications have been set according to the CEP for residual solvent ethyl acetate, azides and known impurity. Moreover, particle size is also specified.

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 (a polyethylene bag placed in an aluminium triplex bag) have been mentioned on the CEP.

GMP compliance of the API manufacture is demonstrated by the applicant.

II.3 Medicinal product

The aim of the development was to develop combination products with rosuvastatin (in the form of calcium salt) and valsartan as active ingredients in one formulation, which are bio-

equivalent to the mono-component products of the originators (i.e. reference products) Crestor® film-coated tablets and Diovan® film-coated tablets.

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 and composition was obtained.

10 mg/80 mg strength: dark pink, round, slightly biconvex, film-coated tablets with bevelled edges, engraved with a mark K4 on one side of the tablet.

20 mg/80 mg strength: dark pink, capsule-shaped, slightly biconvex, film-coated tablets, engraved with a mark K3 on one side of the tablet.

10 mg/160 mg strength: dark pink, oval, biconvex, film-coated tablets, engraved with a mark K2 on one side of the tablet.

20 mg/160 mg strength: light brownish-yellow, oval, biconvex, film-coated tablets, engraved with a mark K1 on one side of the tablet.

The excipients used in the finished product are colloidal anhydrous silica, magnesium stearate, croscarmellose sodium, microcrystalline cellulose, lactose monohydrate, iron oxide (E172), sodium laurilsulfate, povidone K25 and mannitol. The film-coating contains iron oxide (E172), talc, titanium dioxide, macrogol and poly(vinyl alcohol).

All excipients, except the film-coating agent and iron oxides comply with respective Ph. Eur. monograph. Iron oxides comply with USP/NF and are in accordance with Commission Regulation (EU) No 231/2012.

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 for 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 study are presented.

The container closure system of the product is OPA/Al/PVC – Aluminium blisters. 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. The proposed storage condition "store in the original packaging material in order to protect from moisture" is acceptable.

The Summary of Product Characteristics, Patient Information (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 chemical-pharmaceutical points of view the products are approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of both rosuvastatin and valsartan are well known. Since both compounds are widely used, well-known active substances, no further studies non-clinical are required and the applicant provides none. Therefore, overview based on literature review is appropriate. The non-clinical overview has been written by a qualified person and is satisfactory.

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.

Rosuvastatin increases the number of hepatic LDL receptors on the cell-surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of VLDL, thereby reducing the total number of VLDL and LDL particles.

Rosuvastatin reduces elevated LDL-cholesterol, total cholesterol and triglycerides and increases HDL-cholesterol. It also lowers ApoB, nonHDL-C, VLDL-C, VLDL-TG and increases ApoA-I. Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios.

Valsartan is an orally active, potent, and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following AT_1 receptor blockade with valsartan may stimulate the unblocked AT_2 receptor, which appears to counterbalance the effect of the AT_1 receptor. Valsartan does not exhibit any partial agonist activity at the AT_1 receptor and has much (about 20,000 fold) greater affinity for the AT_1 receptor than for the AT_2 receptor. Valsartan is not known to bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Valsartan does not inhibit ACE (also known as kininase II) which converts Ang I to Ang II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with coughing.

III.3 Pharmacokinetics

Absorption: maximum *rosuvastatin* plasma concentrations are achieved a few 5 hours after oral administration. Following oral administration of *valsartan* alone, peak plasma concentrations

of valsartan are reached in a few hours. Food decreases exposure. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

Distribution: *rosuvastatin* is taken up extensively by the liver which is the primary site of cholesterol synthesis and LDL-C clearance. The majority of rosuvastatin is bound to plasma proteins, mainly to albumin. *Valsartan* does not distribute into tissues extensively. It is highly bound to serum proteins, mainly serum 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. *Valsartan* is not biotransformed to a high extent. A hydroxy metabolite has been identified in plasma at low concentrations. This metabolite is pharmacologically inactive.

Elimination: majority 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. The elimination half-life does not increase at higher doses. 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. *Valsartan* shows multiexponential decay kinetics. Valsartan is primarily eliminated by biliary excretion in faeces and renally in urine, mainly as unchanged drug.

III.4 Toxicology

As regards *rosuvastatin*, preclinical data 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.

For *valsartan*, non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential. In rats, maternally toxic doses (600 mg/kg/day) during the last days of gestation and lactation led to lower survival, lower weight gain and delayed development (pinna detachment and ear-canal opening) in the offspring (see section 4.6). These doses in rats (600 mg/kg/day) are approximately 18 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient). In non-clinical safety studies, high doses

of valsartan (200 to 600 mg/kg body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit) and evidence of changes in renal haemodynamics (slightly raised plasma urea, and renal tubular hyperplasia and basophilia in males). These doses in rats (200 and 600 mg/kg/day) are approximately 6 and 18 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient). In marmosets at similar doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy which included raised urea and creatinine. Hypertrophy of the renal juxtaglomerular cells was also seen in both species. All changes were considered to be caused by the pharmacological action of valsartan which produces prolonged hypotension, particularly in marmosets. For therapeutic doses of valsartan in humans, the hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance.

III.5 Ecotoxicology/environmental risk assessment

The combination products are indicated for a substitution indication and as such will replace use of the co-administered single products. The exposure of the environment to rosuvastatin and to valsartan will not increase by use of this products and, consequently, their use would not be expected to have an adverse effect upon the environment. With this regard and on the basis of EMA Guideline on the *Environmental Risk Assessment of Medicinal Products for Human Use* (EMEA/CHMP/SWP/4447/00), a formal environmental risk assessment is not considered necessary.

III.6 Discussion on the non-clinical aspects

Abridged applications avoid the need for repetitive tests on animals. Pharmacodynamic, pharmacokinetic and toxicological properties of both rosuvastatin and valsartan are well known. Literature reviews submitted by the applicant are adequate.

From non-clinical points of view the products are approvable.

IV. CLINICAL ASPECTS

IV.1 Introduction

This application concerns the combinations of rosuvastatin/valsartan 10 mg/80 mg, 20 mg/80 mg, 10 mg/160 mg and 20 mg/160 mg film-coated tablets under trade name Ravalsyo and refers to Article 10b "fix dose combination application". To support the application, the applicant has submitted the reports of two single dose bioequivalence studies with the rosuvastatin/valsartan/rosuvastatin 20 mg/160mg and 10 mg/160mg film-coated tablets under fasting conditions compared with 20 mg Crestor and 160 mg Diovan as well as 10 mg Crestor and 160 mg Diovan given concomitantly. Biowaiver has been requested for the lower. Co-prescription data have also been provided from representative EU member states. The clinical overview has been written by a qualified person and is satisfactory.

IV.2 Pharmacokinetics

IV.2.1 Literature data

Rosuvastatin

The absolute bioavailability of rosuvastatin is approximately 20%. The volume of distribution is about 134 l. Approximately 90% of rosuvastatin is bound to plasma proteins, mainly to albumin. Rosuvastatin undergoes limited metabolism (approximately 10%). About 90% of the rosuvastatin dose is excreted unchanged in the faeces (consisting of absorbed and non-absorbed active substance) and the remaining part, approximately 5% is excreted unchanged in urine. The plasma elimination half-life is approximately 20 hours. It does not increase at higher doses. The geometric mean plasma clearance is approximately 50 litres/hour (coefficient of variation 21.7%). Systemic exposure of rosuvastatin increases in proportion to dose. There are no changes in pharmacokinetic parameters following multiple daily doses.

Valsartan

Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Mean absolute bioavailability is 23%. Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food. The steady-state volume of distribution of valsartan after intravenous administration is about 17 litres, indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (94–97%), mainly serum albumin. Valsartan is not transformed to a high extent as only about 20% of dose is recovered as metabolites. A hydroxy metabolite has been

identified in plasma at low concentrations (less than 10% of the valsartan AUC). This metabolite is pharmacologically inactive. Valsartan shows multiexponential decay kinetics (t½α <1 h and t½ß about 9 h). It is primarily eliminated in faeces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 l/h and its renal clearance is 0.62 l/h (about 30% of total clearance). The half-life of valsartan is 6 hours.

Rosuvastatin/valsartan combination

To assess the pharmacokinetic interaction potential between valsartan and rosuvastatin, knowledge from in vitro and/or mechanistic data on the interaction potential was studied and addressed at the level of liberation, absorption, distribution, metabolism and elimination by literature review. The in vitro data did not indicate any significant interaction between valsartan and rosuvastatin in the different kinetic processes. As the applicant reviewed all the possible ways of the interaction and their own meta-anaysis data did not show any influence on the AUC and C_{max} parameters of valsartan or rosuvastatin, the RMS accepted the overall conclusion about the lack of interaction between the two compounds. Also, there are no interaction data from the clinical practice either, that further implicates the lack of pharmacokinetic interactions.

IV.2.2 Bioequivalence studies

The Applicant has submitted the results of two bioequivalence studies as full report.

1. *Comparative, single-dose, 2-way crossover bioavailability study of rosuvastatin/valsartan fixed dose combination film-coated tablet (Krka, Test) formulation and co-administration of rosuvastatin 20 mg (Crestor®, AstraZeneca UK Limited, UK and valsartan 160 mg (Diovan®, Novartis Pharma GmbH, Germany) as separate film-coated tablets (Reference) in healthy male volunteers under fasting conditions*

Blood samples were collected and analysed for rosuvastatin and valsartan. Determination of rosuvastatin and valsartan in plasma samples was performed using a validated HPLC/MS/MS method.

Pharmacokinetic variables: C_{max}, AUC_t, AUC_i, residual area (R_{AUC}), T_{max}, T_{half} and K_{el} for rosuvastatin and valsartan were determined from individual plasma concentration / time profiles using model-independent approach. Analysis of variance (ANOVA) was performed on the ln-transformed AUC_i, AUC_t and C_{max} parameters for valsartan and rosuvastatin. Consistent with the two one-sided tests for bioequivalence, 90% confidence intervals was calculated for the Test treatment to Reference treatment ratios of least-squares means for parameters AUC_i, AUC_t and C_{max} using ln-transformed data.

Bioequivalence was concluded if the 90% geometric confidence intervals of the ratio (Test/Reference) of least-squares means derived from analyses on the ln-transformed

pharmacokinetic parameters AUC_t and C_{max} for rosuvastatin and valsartan were within 80.00% – 125.00% range. Descriptive statistics were also done for all pharmacokinetic parameters.

The results have adequately shown that the pharmacokinetic parameters of Test tablets are comparable with that of the Reference film-coated tablets. The geometric mean ratios of AUC_t and C_{max} of valsartan and rosuvastatin fall within the 90% confidence interval.

No serious or severe adverse events or deaths occurred during the study. No new safety concerns related to administered formulations were raised during the conduct of this study.

2. *Single dose crossover comparative bioavailability study of rosuvastatin and valsartan following the administration of a fixed dose combination (10 mg/160 mg of rosuvastatin and valsartan) versus individual tablets taken concomitantly (Crestor® 10 mg and Diovan® 160 mg) in healthy male volunteers, fasting state.*

Blood samples were collected and analysed for rosuvastatin and valsartan. Determination of valsartan and rosuvastatin in plasma samples was performed using a validated HPLC/MS/MS method.

Mathematical model and statistical methods of pharmacokinetic parameters: the main absorption and disposition parameters were calculated using a non-compartmental approach with a log-linear terminal phase assumption. The trapezoidal rule was used to estimate area under the curve. The terminal phase estimation was based on maximizing the coefficient of determination. The pharmacokinetic parameters of this trial were C_{max}, T_{max}, AUC_{0-T}, $AUC_{0-\infty}$, residual area, λ_Z and T_{half}. The statistical analysis was based on a parametric ANOVA model of the pharmacokinetic parameters; the two-sided 90% confidence interval of the ratio of geometric means for the C_{max} and AUC_{0-T} and $AUC_{0-\infty}$ was based on ln-transformed data; T_{max} was based on a non-parametric approach.

Criteria for comparative bioavailability: statistical inference of valsartan and rosuvastatin was based on a bioequivalence approach using the following standards, i.e. the ratio of geometric LSmeans with corresponding 90% confidence interval calculated from the exponential of the difference between the Test and Reference treatment for the ln-transformed parameters C_{max} and AUC_{0-T} were all to be within the 80.00 to 125.00% bioequivalence range.

The results have adequately shown that the pharmacokinetic parameters of Test tablets are comparable with that of the Reference film-coated tablets. The geometric mean ratios of AUC_t and C_{max} of valsartan and rosuvastatin fall within the 90% confidence interval.

No serious adverse events and no deaths were reported for any of the subjects enrolled in this study.

Conclusion on the bioequivalence studies

Based on the submitted bioequivalence studies rosuvastatin/valsartan 20 mg/160 mg and 10 mg/160 mg are considered bioequivalent with the same strengths of the reference (Crestor® and Diovan®) film-coated tablets given concomitantly.

Biowaiver

The results of the studies with the 20 mg/160 mg and 10 mg/160 mg formulations can be extrapolated to other strengths 10 mg/80 mg and 20 mg/80 mg, according to conditions in *Guideline on the Investigation of Bioequivalence* CPMP/EWP/QWP/1401/98 Rev. 1/corr*, section 4.1.6.

IV.3 Pharmacodynamics

Rosuvastatin

Rosuvastatin is a selective, reversible competitive inhibitor of HMG-CoA reductase, the enzyme responsible for the conversion of HMG-CoA reductase to mevalonate early in the cholesterol biosynthetic pathway. Rosuvastatin thus decreases hepatic biosynthesis of cholesterol, which, in turn, leads to a decrease in hepatocellular cholesterol. Hepatocytes compensate by increasing the synthesis of LDL receptors to increase hepatic LDL reuptake from the circulation. This process reduces the serum LDL concentration by increasing the fractional catabolic rate of LDL.

Rosuvastatin shares the mechanism of action with other statins but has the strongest lipid-lowering effect of the class. Due to specific structural features it has higher affinity (four times the original substrate HMG- CoA) for the specific binding site of HMG-CoA reductase plus additional enzyme-binding interactions that cause tighter binding. Its relatively high hydrophilicity enables rosuvastatin to be primarily distributed in hepatocytes, its main site of action, while at the same time the cholesterol inhibition in non-hepatic tissues was about 1000 times lower than in hepatocytes. Furthermore, the OATP-C, which is strongly expressed on the basolateral membrane of hepatocytes represents an important transporting mechanism by which rosuvastatin is selectively delivered to HMG-CoA reductase within the hepatocytes. Its affinity for OATP-C is may contribute to the explanation for its low IC50.

Beside the therapeutic effects related to lipid-lowering action, rosuvastatin has other effects that may also contribute to its anti-atherosclerotic action. These so- called pleotropic effects have also been identified in other statins. They encompass various beneficial actions on different organic systems such as improvement of endothelial function, reduction in osteoporosis and risks of fracture, reduction in blood pressure, diminished vascular inflammation, reduced trombogenicity and reduced incidence of diabetes. Some of these effects have also been demonstrated with rosuvastatin.

Valsartan

Valsartan is a nonpeptide, orally active, and specific of angiotensin II (AII) antagonist or angiotensin receptor blocker (ARB). It selectively, competitive and insurmountable inhibits the actions of AII at the AII type 1 (AT_1) receptor subtype which is responsible for most of the known effects of AII. It blocks the vasoconstrictor and aldosterone-secreting effects of AII by selectively blocking the binding of AII to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for AII synthesis. Blockade of the AII receptor inhibits the negative regulatory feedback of AII on renin secretion, but the resulting increased plasma renin activity (PRA) and AII circulating levels do not overcome the effect of valsartan on blood pressure. Because valsartan does not inhibit ACE (kininase II) it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Even in high concentrations, valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation

Rosuvastatin/valsartan combination

The pharmacodynamics of both active substances are well known. The combination in the clinical practice may be beneficial in terms of better perspective of patients suffering from both hypertension and hyperlipidaemia. With the combination two cardiovascular risk factors are aimed to reduce. However, rosuvastatin/valsartan of Krka fixed dose combination is for substitution indication only therefore no clinical efficacy studies are necessary to prove the better efficacy of the combination compared to the monotherapy treatments.

The applicant has summarised the clinical efficacy findings from the literature with valsartan and rosuvastatin given concomitantly. Furthermore, the efficacy results of the monotherapy both with valsartan and rosuvastatin was also summarised. Since the combination is for substitution only the literature summary is sufficient from a regulatory point of view.

IV.4 Clinical efficacy

In order to further justify the substitution indication of the Ravalsyo rosuvastatin/valsartan fix-dose combination film-coated tablets the applicant has summarized the results of the published clinical studies.

The studies were designed to detect changes in the acutely measurable parameters such as blood pressure and lipid profile. They found no interaction between valsartan and rosuvastatin on these parameters. Since the combination is for substitution only, the co-administration of rosuvastatin and valsartan is based on the physicians' decisions who follow the recommendations of cardiology guidelines. The co-administration of RAAS antagonists and statins is a common practice. There are clinical data clearly supporting the combination treatment.

In order to further substantiate the clinical need for the fixed dose combinations of rosuvastatin and valsartan in the substitution indication the applicant has provided co-prescription data from

several EU countries. These co-prescription data show an increase. For no data have been available from all the CMSS, the applicant has provided an estimation of concomitant use of rosuvastatin and valsartan. The estimation is based on the lowest sold amounts of the active substances. Though it is rather strict, it assumes the same medical practice in the CMSS as in Hungary. Although this is not proven, the RMS considered the approach acceptable since the prescription tendencies are unequivocally increasing.

IV.5 Clinical safety

The clinical safety of both rosuvastatin and valsartan has been well established. Since the combination is for substitution only, no new data were needed from a regulatory point of view.

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
	Hepatic effects: increased transaminases, hepatitis, jaundice
	Diabetes mellitus
	Stevens-Johnson syndrome/toxic epidermal necrolysis
	Renal impairment and renal failure
	Hyperkalemia
	Fetotoxicity and neonatal toxicity
Important potential risks	Interstitial lung disease
	Teratogenicity
	Off label use
Missing information	Use in paediatric population
	Use in patients with a creatinine clearance < 10 ml/min
	Use in patients undergoing dialysis
	Use in patients with recent kidney transplantation
	Long-term safety of the combination

Routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to Ravalsyo (rosuvastatin/valsartan) 10 mg/80 mg, 20 mg/80

mg, 10 mg/160 mg and 20 mg/160 mg film-coated tablets. No additional activities are proposed.

Routine risk minimisation 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 Ravalsyo (rosuvastatin/valsartan) 10 mg/80 mg, 20 mg/80 mg, 10 mg/160 mg and 20 mg/160 mg 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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 3 years following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

IV.7 Discussion on the clinical aspects

The application contains an adequate review of published clinical data. In addition, the bioequivalence between rosuvastatin/valsartan Krka 20 mg/160 mg and 10 mg/160 mg film-coated tablets as well as concomitantly used Crestor® 20mg or 10mg and Diovan® 160 mg film-coated tablets and has been established. The biowaiver for the strengths 20 mg/80 mg and 10 mg/80mg strengths can also be granted. The increasing number of co-prescriptions may also justify the need of such combinations. Approval can be recommended from the clinical point of view.

The Summary of Product Characteristics and Package Leaflet are in line with those of the originators (Crestor® and Diovan®), therefore, are acceptable.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present applications concern Ravalsyo film-coated tablets, fixed combinations of rosuvastatin/valsartan 10 mg/80 mg, 20 mg/80 mg, 10 mg/160 mg and 20 mg/160 mg. The applicant and the future holder of authorisation is Krka d.d.

The products are indicated for the following conditions: as substitution therapy for those patients who are adequately controlled with rosuvastatin and valsartan given concurrently, at the same dose level as in the combination for the treatment of hypertension in adult patients who are estimated to have a high risk for a first cardiovascular event (for prevention of major cardiovascular events) or with one of the following coincident conditions:

- primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIb),
- homozygous familial hypercholesterolaemia.

The application was submitted according to Article 10b of Directive 2001/83/EC ("fixed-dose combination application"). The applicant identified two monocomponent reference products: Crestor® (rosuvastatin, AstraZeneca) and Diovan® (valsartan, Novartis). The bioequivalence between the submitted test and the concomitantly given reference products has been adequately proven. The results can be extended to the lower strengths. Moreover, the concomitant use of the monocomponents has been proven by co-prescription data originated from several EU member states.

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 Ravalsyo 10 mg/80 mg, 20 mg/80 mg, 10 mg/160 mg and 20mg/160 mg film-coated tablets.

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