Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rosuvastatin/amlodipine Krka 15mg/10mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 15 mg rosuvastatin (as rosuvastatin calcium) and 10 mg amlodipine (as amlodipine besylate).

Excipient with known effect:
Each 15 mg/10 mg film-coated tablet contains 84 mg anhydrous lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Off pink, round, slightly biconvex, film-coated tablets with bevelled edges, engraved with mark 15-10 on one side of the tablet with a diameter of approx. 10 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Rosuvastatin/amlodipine Krka is indicated as substitution therapy for those patients who are adequately controlled with rosuvastatin and amlodipine 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) as an adjunct to correction of other risk factors or with one of the following coincident conditions:
- primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIb) as an adjunct to diet when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate
- homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate.

4.2 Posology and method of administration

Posology

Before treatment initiation the patient should be placed on a standard cholesterol-lowering diet that should continue during treatment.

The recommended dose of Rosuvastatin/amlodipine Krka is one tablet per day.

The fixed dose combination is not suitable for initial therapy.

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

If the change of posology is required for any of the active substances of the fixed combination due to any reason (e.g. newly diagnosed related illness, change of the condition of the patient or due to drug interaction), the individual components should be used again in order to determine the posology.

In hypertensive patients, amlodipine has been used in combination with a thiazide diuretic, alpha blocker, beta blocker, or an angiotensin converting enzyme inhibitor.

No dose adjustment of amlodipine is required upon concomitant administration of thiazide diuretics, beta blockers, and angiotensin-converting enzyme inhibitors.

Elderly

No dosage adjustment is required.

Renal impairment

No dosage adjustment is required for patients with mild to moderate renal impairment.

The use of Rosuvastatin/amlodipine Krka in patients with severe renal impairment is contraindicated for all doses. (See section 4.3 and section 5.2).

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

Hepatic impairment

Dosage recommendations of amlodipine have not been established in patients with mild to moderate hepatic impairment. The pharmacokinetics of amlodipine has not been studied in severe hepatic impairment.

There was no increase in systemic exposure to rosuvastatin in subjects with Child-Pugh scores of 7 or below. However, increased systemic exposure has been observed in subjects with Child-Pugh scores of 8 and 9 (see section 5.2). In these patients an assessment of renal function should be considered (see section 4.4). There is no experience in subjects with Child-Pugh scores above 9. Rosuvastatin/amlodipine Krka is contraindicated in patients with active liver disease (see section 4.3).

Ethnic Differences
Increased systemic exposure to rosuvastatin has been seen in Asian subjects (see section 5.2).

Genetic polymorphisms
Specific types of genetic polymorphisms are known that can lead to increased rosuvastatin exposure (see section 5.2). For patients who are known to have such specific types of polymorphisms, a lower daily dose of rosuvastatin is recommended.

Concomitant therapy
Rosuvastatin is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when rosuvastatin is administered concomitantly with certain medicinal products that may increase the plasma concentration of rosuvastatin due to interactions with these transporter proteins (e.g. ciclosporin and certain protease inhibitors including combinations of ritonavir with atazanavir, lopinavir, and/or tipranavir; see sections 4.4 and 4.5). Whenever possible, alternative medications should be considered, and, if necessary, consider temporarily discontinuing rosuvastatin therapy. In situations where co-administration of these medicinal products with rosuvastatin is unavoidable, the benefit and the risk of concurrent treatment and rosuvastatin dosing adjustments should be carefully considered (see section 4.5).

Paediatric population

The safety and efficacy of Rosuvastatin/amlodipine in children and adolescents below 18 years have not been established. Rosuvastatin/amlodipine Krka is not recommended for use in patients aged below 18 years

Method of administration

Rosuvastatin/amlodipine Krka tablets should be taken at any time of the day and can be taken with or without food. They should be swallowed with liquid and should not be chewed.

4.3 Contraindications

Linked to rosuvastatin component:
- Active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3 x the upper limit of normal (ULN).
- Severe renal impairment (creatinine clearance <30 ml/min).
- Myopathy.
- Concomitant ciclosporin treatment.
- Pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures.
- Hypersensitivity to rosuvastatin.

Linked to amlodipine component:
- Severe hypotension.
- Shock (including cardiogenic shock).
- Obstruction of the outflow tract of the left ventricle (e.g., high grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction.
- Hypersensitivity to amlodipine and dihydropyridine derivatives.

Linked to Rosuvastatin/amlodipine Krka:
- Hypersensitivity to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Renal effects
Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with higher doses of rosuvastatin, in particular 40 mg, where it was transient or intermittent in most cases. Proteinuria has not been shown to be predictive of acute or progressive renal disease (see section 4.8). The reporting rate for serious renal events in post-marketing use is higher at the 40 mg dose.

Skeletal muscle effects
Effects on skeletal muscle e.g. myalgia, myopathy and, rarely, rhabdomyolysis have been reported in rosuvastatin-treated patients with all doses and in particular with doses >20 mg. Very rare cases of rhabdomyolysis have been reported with the use of ezetimibe in combination with HMG-CoA reductase inhibitors. A pharmacodynamic interaction cannot be excluded (see section 4.5) and caution should be exercised with their combined use.

Creatine kinase measurement
Creatine Kinase (CK) should not be measured following strenuous exercise or in the presence of a plausible alternative cause of CK increase which may confound interpretation of the result. If CK levels are significantly elevated at baseline (>5xULN) a confirmatory test should be carried out within 5 – 7 days. If the repeat test confirms a baseline CK >5xULN, treatment should not be started.

Before treatment
Rosuvastatin/amlodipine Krka, as with other HMG-CoA reductase inhibitor containing products, should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis due to rosuvastatin component. Such factors include:
- renal impairment
- hypothyroidism
- personal or family history of hereditary muscular disorders
- previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate
- alcohol abuse
- age >70 years
- situations where an increase in plasma levels may occur (see sections 4.2, 4.5 and 5.2)
- concomitant use of fibrates.

In such patients the risk of treatment should be considered in relation to possible benefit and clinical monitoring is recommended. If CK levels are significantly elevated at baseline (>5xULN) treatment should not be started.

Whilst on treatment
Patients should be asked to report inexplicable muscle pain, weakness or cramps immediately, particularly if associated with malaise or fever. CK levels should be measured in these patients. Therapy should be discontinued if CK levels are markedly elevated (>5xULN) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are ≤5x ULN). If symptoms resolve and CK levels return to normal, then consideration should be given to re-introducing rosuvastatin or an alternative HMG-CoA reductase inhibitor at the lowest dose with close monitoring. Routine monitoring of CK levels in asymptomatic patients is not warranted. There have been very rare reports of an immune-mediated necrotising myopathy (IMNM) during or after treatment with statins, including rosuvastatin. IMNM is clinically characterized by proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.

In clinical trials there was no evidence of increased skeletal muscle effects in the small number of patients dosed with rosuvastatin and concomitant therapy. However, an increase in the incidence of myositis and myopathy has been seen in patients receiving other HMG-CoA reductase inhibitors together with fibric acid derivatives including gemfibrozil, ciclosporin, nicotinic acid, azole antifungals, protease inhibitors and macrolide antibiotics. Gemfibrozil increases the risk of myopathy when given concomitantly with some HMG-CoA reductase inhibitors. Therefore, the combination of Rosuvastatin/amlodipine Krka and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of Rosuvastatin/amlodipine Krka with fibrates or niacin should be carefully weighed against the potential risks of such combinations. (See section 4.5 and section 4.8.)

Rosuvastatin/amlodipine Krka must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins in combination (see section 4.5). The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness.

Statin therapy may be re-introduced seven days after the last dose of fusidic acid.

In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g., for the treatment of severe infections, the need for co-administration of Rosuvastatin/amlodipine Krka and fusidic acid should only be considered on a case by case basis and under close medical supervision.

Rosuvastatin/amlodipine Krka should not be used in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g. sepsis, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders; or uncontrolled seizures).

Liver effects
As with other HMG-CoA reductase inhibitor containing products, Rosuvastatin/amlodipine Krka should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease.

It is recommended that liver function tests be carried out prior to, and 3 months following, the initiation of rosuvastatin treatment. Rosuvastatin/amlodipine Krka should be discontinued or the dose of Rosuvastatin/amlodipine Krka reduced if the level of serum transaminases is greater than 3 times the upper limit of normal.

In patients with secondary hypercholesterolaemia caused by hypothyroidism or nephrotic syndrome, the underlying disease should be treated prior to initiating therapy with Rosuvastatin/amlodipine Krka.

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

Ethnic differences
Pharmacokinetic studies show an increase in exposure in Asian subjects compared with Caucasians (see section 4.2, section 4.3 and section 5.2).

Protease inhibitors
Increased systemic exposure to rosuvastatin has been observed in subjects receiving rosuvastatin concomitantly with various protease inhibitors in combination with ritonavir. Consideration should be given both to the benefit of lipid lowering by use of rosuvastatin in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up titrating rosuvastatin doses in patients treated with protease inhibitors. The concomitant use with protease inhibitors is not recommended unless the dose of rosuvastatin is adjusted. (see sections 4.2 and 4.5).

Interstitial lung disease
Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected that a patient has developed interstitial lung disease, statin therapy should be discontinued.

Diabetes mellitus
Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI > 30 kg/m2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

In the JUPITER study, the reported overall frequency of diabetes mellitus was 2.8% in rosuvastatin and 2.3% in placebo, mostly in patients with fasting glucose 5.6 to 6.9 mmol/L.

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

Patients with cardiac failure
Patients with heart failure should be treated with caution due to amlodipine component. In a long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group(see section 5.1). Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

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

Because of the rosuvastatin component the use of Rosuvastatin/amlodipine Krka in patients with severe renal impairment is contraindicated for all doses. (See section 4.3 and section 5.2).

Lactose
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

Linked to rosuvastatin component

Effect of co-administered medicinal products on rosuvastatin

Transporter protein inhibitors: Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter OATP1B1 and efflux transporter BCRP. Concomitant administration of rosuvastatin with medicinal products that are inhibitors of these transporter proteins may result in increased rosuvastatin plasma concentrations and an increased risk of myopathy (see sections 4.2, 4.4, and 4.5 Table 1).

Ciclosporin: During concomitant treatment with rosuvastatin and ciclosporin, rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers (see Table 1). Rosuvastatin is contraindicated in patients receiving concomitant ciclosporin (see section 4.3). Concomitant administration did not affect plasma concentrations of ciclosporin.

Protease inhibitors: Although the exact mechanism of interaction is unknown, concomitant protease inhibitor use may strongly increase rosuvastatin exposure (see Table 1). For instance, in a pharmacokinetic study, co-administration of 10 mg rosuvastatin and a combination product of two protease inhibitors (300 mg atazanavir / 100 mg ritonavir) in healthy volunteers was associated with an approximately three-fold and seven-fold increase in rosuvastatin steady-state AUC and C_{max} respectively. The concomitant use of rosuvastatin and some protease inhibitor combinations may be considered after careful consideration of rosuvastatin dose adjustments based on the expected increase in rosuvastatin exposure (see sections 4.2, 4.4, and 4.5 Table 1).

Gemfibrozil and other lipid-lowering products: Concomitant use of rosuvastatin and gemfibrozil resulted in a 2-fold increase in rosuvastatin C_{max} and AUC (see section 4.4).
Based on data from specific interaction studies no pharmacokinetic relevant interaction with fenofibrate is expected, however a pharmacodynamic interaction may occur. Gemfibrozil, fenofibrate, other fibrates and lipid lowering doses (> or equal to 1g/day) of niacin (nicotinic acid) increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone.

Ezetimibe: Concomitant use of 10 mg rosuvastatin and 10 mg ezetimibe resulted in a 1.2-fold increase in AUC of rosuvastatin in hypercholesterolaemic subjects (Table 1). However, a pharmacodynamic interaction, in terms of adverse effects, between Rosuvastatin/amlodipine Krka and ezetimibe cannot be ruled out (see section 4.4).

Antacid: The simultaneous dosing of rosuvastatin with an antacid suspension containing aluminium and magnesium hydroxide resulted in a decrease in rosuvastatin plasma concentration of approximately 50%. This effect was mitigated when the antacid was dosed 2 hours after Rosuvastatin/amlodipine Krka. The clinical relevance of this interaction has not been studied.

Erythromycin: Concomitant use of rosuvastatin and erythromycin resulted in a 20% decrease in AUC and a 30% decrease in C_{max} of rosuvastatin. This interaction may be caused by the increase in gut motility caused by erythromycin.

Cytochrome P450 enzymes: Results from *in vitro* and *in vivo* studies show that rosuvastatin is neither an inhibitor nor an inducer of cytochrome P450 isoenzymes. In addition, rosuvastatin is a poor substrate for these isoenzymes. Therefore, drug interactions resulting from cytochrome P450-mediated metabolism are not expected. No clinically relevant interactions have been observed between rosuvastatin and either fluconazole (an inhibitor of CYP2C9 and CYP3A4) or ketoconazole (an inhibitor of CYP2A6 and CYP3A4).

Interactions requiring rosuvastatin dose adjustments (see also Table 1): When it is necessary to co-administer rosuvastatin with other medicinal products known to increase exposure to rosuvastatin, doses of rosuvastatin should be adjusted. The maximum daily dose of rosuvastatin should be adjusted so that the expected rosuvastatin exposure would not likely exceed that of a 40 mg daily dose of rosuvastatin taken without interacting medicinal products, for example a 20 mg dose of rosuvastatin with gemfibrozil (1.9-fold increase), and a 10 mg dose of rosuvastatin with combination atazanavir/ritonavir (3.1-fold increase).

Table 1. Effect of co-administered medicinal products on rosuvastatin exposure (AUC; in order of decreasing magnitude) from published clinical trials		
Interacting drug dose regimen	**Rosuvastatin dose regimen**	**Change in rosuvastatin AUC***
Ciclosporin 75 mg BID to 200 mg BID, 6 months	10 mg OD, 10 days	7.1-fold ↑
Atazanavir 300 mg/ritonavir 100 mg OD, 8 days	10 mg, single dose	3.1-fold ↑
Simeprevir 150 mg OD, 7 days	10 mg, single dose	2.8-fold ↑
Lopinavir 400 mg/ritonavir 100 mg BID, 17 days	20 mg OD, 7 days	2.1-fold ↑
Clopidogrel 300 mg loading, followed by 75 mg at 24 hours	20 mg, single dose	2-fold ↑
Gemfibrozil 600 mg BID, 7 days	80 mg, single dose	1.9-fold ↑
Eltrombopag 75 mg OD, 5 days	10 mg, single dose	1.6-fold ↑
Darunavir 600 mg/ritonavir 100 mg BID, 7 days	10 mg OD, 7 days	1.5-fold ↑
Tipranavir 500 mg/ritonavir 200 mg BID, 11 days	10 mg, single dose	1.4-fold ↑
Dronedarone 400 mg BID	Not available	1.4-fold ↑
Itraconazole 200 mg OD, 5 days	10 mg, single dose	1.4-fold ↑**

Ezetimibe 10 mg OD, 14 days	10 mg, OD, 14 days	1.2-fold ↑**
Fosamprenavir 700 mg/ritonavir 100 mg BID, 8 days	10 mg, single dose	↔
Aleglitazar 0.3 mg, 7 days	40 mg, 7 days	↔
Silymarin 140 mg TID, 5 days	10 mg, single dose	↔
Fenofibrate 67 mg TID, 7 days	10 mg, 7 days	↔
Rifampin 450 mg OD, 7 days	20 mg, single dose	↔
Ketoconazole 200 mg BID, 7 days	80 mg, single dose	↔
Fluconazole 200 mg OD, 11 days	80 mg, single dose	↔
Erythromycin 500 mg QID, 7 days	80 mg, single dose	20% ↓
Baicalin 50 mg TID, 14 days	20 mg, single dose	47% ↓
*Data given as x-fold change represent a simple ratio between co-administration and rosuvastatin alone. Data given as % change represent % difference relative to rosuvastatin alone. Increase is indicated as "↑", no change as "↔", decrease as "↓". **Several interaction studies have been performed at different Crestor dosages, the table shows the most significant ratio OD = once daily; BID = twice daily; TID = three times daily; QID = four times daily		

Effect of rosuvastatin on co-administered medicinal products

Vitamin K antagonists: As with other HMG-CoA reductase inhibitors, the initiation of treatment or dosage up-titration of rosuvastatin in patients treated concomitantly with vitamin K antagonists (e.g. warfarin or another coumarin anticoagulant) may result in an increase in International Normalised Ratio (INR). Discontinuation or down-titration of rosuvastatin may result in a decrease in INR. In such situations, appropriate monitoring of INR is desirable.

Oral contraceptive/hormone replacement therapy (HRT): Concomitant use of rosuvastatin and an oral contraceptive resulted in an increase in ethinyl estradiol and norgestrel AUC of 26% and 34%, respectively. These increased plasma levels should be considered when selecting oral contraceptive doses. There are no pharmacokinetic data available in subjects taking concomitant rosuvastatin and HRT and therefore a similar effect cannot be excluded. However, the combination has been extensively used in women in clinical trials and was well tolerated.

Other medicinal products: Based on data from specific interaction studies no clinically relevant interaction with digoxin is expected.

Fusidic Acid: The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. The mechanism of this interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination.

If treatment with systemic fusidic acid is necessary, rosuvastatin treatment should be discontinued throughout the duration of the fusidic acid treatment. Also see section 4.4

Linked to amlodipine component

Effects of other medicinal products on amlodipine

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

CYP3A4 inducers: There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g., rifampicin, hypericum perforatum) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

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

Dantrolene (infusion): In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Effects of amlodipine on other medicinal products

The blood pressure lowering effects of amlodipine add to the blood pressure-lowering effects of other medicinal products with antihypertensive properties.

Tacrolimus: There is a risk of increased tacrolimus blood levels when co-administered with amlodipine. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

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

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

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

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

4.6 Fertility, pregnancy and lactation

Rosuvastatin/amlodipine Krka is contraindicated in pregnancy and lactation.
(See section 4.3)

Pregnancy

Women of child bearing potential should use appropriate contraceptive measures.
Since cholesterol and other products of cholesterol biosynthesis are essential for the development of the foetus, the potential risk from inhibition of HMG-CoA reductase outweighs the advantage of treatment during pregnancy. Animal studies provide limited evidence of reproductive toxicity (see section 5.3). If a patient becomes pregnant during use of this product, treatment should be discontinued immediately.

The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses (see section 5.3). Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

Breast-feeding
Breastfeeding is contraindicated during administration of Rosuvastatin/amlodipine Krka. It is not known whether amlodipine is excreted in breast milk.

Rosuvastatin is excreted in the milk of rats. There are no data with respect to excretion in milk in humans. (See section 4.3).

Fertility
Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Rosuvastatin/amlodipine Krka can have minor or moderate influence on the ability to drive and use machines.

Studies to determine the effect of rosuvastatin on the ability to drive and use machines have not been conducted. However, based on its pharmacodynamic properties, rosuvastatin is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that dizziness may occur during treatment.

Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired. Caution is recommended.

4.8 Undesirable effects

- Very common (≥1/10)
- Common (≥ 1/100 to < 1/10)
- Uncommon (≥ 1/1,000 to < 1/100)
- Rare (≥ 1/10,000 to < 1/1,000)
- Very rare (< 1/10,000)
- Not known (cannot be estimated from the available data)

Tabulated list of adverse reactions

MedDRA System Organ Class	**Undesirable Effects**	**Frequency**	
		Rosuvastatin	**Amlodipine**
Blood and lymphatic system disorders	Leukocytopenia, thrombocytopenia	-	Very rare
	Thrombocytopenia	Rare	-
Immune system disorders	Allergic reactions	-	Very rare
	Hypersensitivity reactions including angioedema	Rare	-
Metabolism and nutrition disorders	Hyperglycaemia	-	Very rare
Endocrine disorders	Diabetes mellitus[1]	Common	-
Psychiatric disorders	Sleep disorders (insomnia, nightmares), depression	Not known	Uncommon
	Mood changes (including anxiety)	-	Uncommon
	Confusion	-	Rare
	Depression	Not known	-
Nervous system disorders	Dizziness, headache	Common	Common
	Syncope	-	Uncommon
	Somnolence	-	Common
	Tremor, dysgeusia, hypoesthesia, paresthesia	-	Uncommon
	Hypertonia	-	Very rare
	Peripheral neuropathy	Not known	Very rare
	Polyneuropathy, memory loss	Very rare	-
	Extrapyramidal disorder	-	Not known
Eye disorders	Visual disturbance (including diplopia)	-	Common
Ear and labyrinth disorders	Tinnitus	-	Uncommon
Cardiac disorders	Palpitations	-	Common
	Arrhythmia, (including bradycardia, ventricular tachycardia and atrial fibrillation)	-	Uncommon
	Myocardial infarction,	-	Very rare
Vascular disorders	Flushing	-	Common
	Hypotension	-	Uncommon

	Vasculitis	-	Very rare
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Not known	Common
	Rhinitis	-	Uncommon
	Cough	Not known	Uncommon
Gastrointestinal disorders	Vomiting	-	Uncommon
	Abdominal pain	Common	Common
	Nausea	Common	Common
	Dyspepsia, altered bowel habits (including diarrhoea and constipation)	-	Common
	Dry mouth	-	Uncommon
	Gastritis, gingival hyperplasia	-	Very rare
	Constipation	Common	-
	Pancreatitis	Rare	Very rare
	Diarrhoea	Not known	-
Hepatobiliary disorders	Hepatitis	Very rare	Very rare
	Jaundice	Very rare	Very rare
	Hepatic enzyme increased*	-	Very rare
	Increased hepatic transaminases	Rare	-
Skin and subcutaneous tissue disorders	Alopecia	-	Uncommon
	Purpura, skin discolouration, hyperhidrosis, exanthema	-	Uncommon
	Angioedema, erythema multiforme, exfoliative dermatitis, Quincke oedema, photosensitivity	-	Very rare
	Rash	Uncommon	Uncommon
	Pruritis	Uncommon	Uncommon
	Urticaria	Uncommon	Uncommon
	Stevens-Johnson syndrome	Not known	Very rare
Musculoskeletal and connective tissue disorders	Ankle swelling	-	Common
	Back pain	-	Uncommon
	Muscle cramps	-	Common
	Myalgia	Common	Uncommon
	Myopathy (including myositis)	Rare	-
	Rhabdomyolysis	Rare	-
	Arthralgia	Very rare	Uncommon
	Immune-mediated necrotising myopathy	Not known	-
	Tendon disorders, sometimes complicated by rupture	Not known	-
Renal and urinary disorders	Micturition disorder, nocturia, increased urinary frequency	-	Uncommon
	Haematuria	Very rare	-
Reproductive system and breast disorders	Potency disorders (impotence)	-	Uncommon
	Gynaecomastia	Very rare	Uncommon
General disorders and administration site conditions	Asthenia	Common	Common
	Fatigue	-	Common
	Oedema	Not known	Very common
	Chest pain, pain, malaise	-	Uncommon
Investigations	Weight increase, weight decrease	-	Uncommon

[1] Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI >30 kg/m2, raised triglycerides, history of hypertension).
*mostly consistent with cholestasis

As with other HMG-CoA reductase inhibitors, the incidence of adverse drug reactions tends to be dose dependent.

Description of selected adverse reactions

Renal Effects: Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with rosuvastatin. Shifts in urine protein from none or trace to ++ or more were seen in <1% of patients at some time during treatment with 10 and 20 mg, and in approximately 3% of patients treated with 40 mg. A minor increase in shift from none or trace to + was observed with the 20 mg dose. In most cases, proteinuria decreases or disappears spontaneously on continued therapy. Review of data from clinical trials and post-marketing experience to date has not identified a causal association between proteinuria and acute or progressive renal disease.

Haematuria has been observed in patients treated with rosuvastatin and clinical trial data show that the occurrence is low.

Skeletal muscle effects: Effects on skeletal muscle e.g. myalgia, myopathy (including myositis) and, rarely, rhabdomyolysis with and without acute renal failure have been reported in rosuvastatin-treated patients with all doses and in particular with doses > 20 mg.

A dose-related increase in CK levels has been observed in patients taking rosuvastatin; the majority of cases were mild, asymptomatic and transient. If CK levels are elevated (>5xULN), treatment should be discontinued (see section 4.4).

Liver Effects: As with other HMG-CoA reductase inhibitors, a dose-related increase in transaminases has been observed in a small number of patients taking rosuvastatin; the majority of cases were mild, asymptomatic and transient.

The following adverse events have been reported with some statins:
- Sexual dysfunction
- Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4)

The reporting rates for rhabdomyolysis, serious renal events and serious hepatic events (consisting mainly of increased hepatic transaminases) is higher at the 40 mg dose.

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

4.9 Overdose

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

Management
If overdose occurs, the treatment with Rosuvastatin/amlodipine Krka should be stopped and supportive and symptomatic treatment should be provided. Liver function and CK levels should be monitored.

Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG CoA reductase inhibitors, other combinations, ATC code: C10BX09.

Rosuvastatin

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.

Amlodipine

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

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

1. Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.

2. The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

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

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1mm ST segment depression and decreases both angina attack frequency and glyceryl trinitrate tablet consumption.

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

5.2 Pharmacokinetic properties

Absorption, distribution

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.

Amlodipine

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 l/kg. In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins. The bioavailability of amlodipine is not affected by food intake.

Biotransformation, elimination

Rosuvastatin
Rosuvastatin undergoes limited metabolism (approximately 10%). *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 Ndesmethyl 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.

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

Linearity/non-linearity
Systemic exposure of rosuvastatin increases in proportion to dose. There are no changes in pharmacokinetic parameters following multiple daily doses.

Special populations:

Age and sex
There was no clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin in adults. The pharmacokinetics of rosuvastatin in children and adolescents with heterozygous familial hypercholesterolaemia was similar to that of adult volunteers.

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

Race
Pharmacokinetic studies show an approximate 2-fold elevation in median AUC and C_{max} of rosuvastatin in Asian subjects (Japanese, Chinese, Filipino, Vietnamese and Koreans) compared with Caucasians; Asian-Indians show an approximate 1.3-fold elevation in median AUC and C_{max}. A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics between Caucasian and Black groups.

Renal impairment
In a study in subjects with varying degrees of renal impairment, mild to moderate renal disease had no influence on plasma concentration of rosuvastatin or the N-desmethyl metabolite. Subjects with severe impairment (CrCl < 30 ml/min) had a 3-fold increase in plasma concentration and a 9-fold increase in the N-desmethyl metabolite concentration compared to healthy volunteers. Steady-state plasma concentrations of rosuvastatin in subjects undergoing haemodialysis were approximately 50% greater compared to healthy volunteers.

Hepatic impairment
In a study with subjects with varying degrees of hepatic impairment there was no evidence of increased exposure to rosuvastatin in subjects with Child-Pugh scores of 7 or below. However, two subjects with Child-Pugh scores of 8 and 9 showed

an increase in systemic exposure of at least 2-fold compared to subjects with lower Child-Pugh scores. There is no experience in subjects with Child-Pugh scores above 9.

Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40-60%.

5.3 Preclinical safety data

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.

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

Impairment of fertility
There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

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

*Based on patient weight of 50 kg

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose, microcrystalline
Lactose, anhydrous
Crospovidone type A
Silica, colloidal anhydrous
Magnesium stearate

Film coating:
Poly(vinyl) alcohol
Titanium dioxide (E171)
Macrogol 3350
Talc
Iron oxide yellow (E172)
Iron oxide red (E172)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store in the original package in order to protect from light and moisture.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Blister (OPA/Alu/PVC//Alu): 10, 28, 30, 56, 60, 90, 98 and 100 film-coated tablets, in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA1347/053/006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 22nd January 2016

10 DATE OF REVISION OF THE TEXT

December 2016