Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rosuvastatin/Ezetimibe KRKA 10 mg/10 mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg rosuvastatin (as rosuvastatin calcium) and 10 mg ezetimibe.

Excipients with known effect:

Each 10 mg/10 mg film-coated tablet contains 62.85 mg lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Pale brownish-yellow to pale brown-yellow round, slightly biconvex film-coated tablets with bevelled edges, engraved with mark R2 on one side of the tablet. Tablet diameter: approximately 10 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary Hypercholesterolaemia/Homozygous Familial Hypercholesterolaemia
Rosuvastatin/Ezetimibe KRKA is indicated as substitution therapy adjunctive to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) for use in adult patients with primary hypercholesterolaemia (heterozygous familial and nonfamilial) or homozygous familial hypercholesterolaemia, who are adequately controlled with the individual substances given concurrently at same dose level as in the fixed dose combination, but as separate products.

Prevention of Cardiovascular Events
Rosuvastatin/Ezetimibe KRKA is indicated as substitution therapy in adult patients who are adequately controlled with rosuvastatin and ezetimibe given concurrently, at the same dose level as in the fixed dose combination, but as separate products to reduce the risk of cardiovascular events in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS).

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/Ezetimibe KRKA is one tablet per day.

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

Rosuvastatin/Ezetimibe KRKA is not suitable for initial therapy. Treatment initiation or dose adjustment if necessary should only be done with the monocomponents and after setting the appropriate doses the switch to the fixed dose combination of the appropriate strength is possible.

Co-administration with bile acid sequestrants
Dosing of Rosuvastatin/Ezetimibe KRKA should occur either at least 2 hours before or not less than 4 hours after administration of a bile acid sequestrant (see section 4.5).

Special populations

Elderly
A start dose of rosuvastatin 5 mg is recommended in patients >70 years (see section 4.4). No other dose adjustment is necessary in relation to age.

Renal impairment
No dose adjustment is necessary in patients with mild renal impairment.
The recommended start dose of rosuvastatin is 5 mg in patients with moderate renal impairment (creatinine clearance <60 ml/min). The 40 mg/10 mg dose is contraindicated in patients with moderate renal impairment. The use of Rosuvastatin/Ezetimibe KRKA in patients with severe renal impairment is contraindicated for all doses (see sections 4.3 and 5.2).

Hepatic impairment
No dose adjustment is required in patients with mild hepatic insufficiency (Child Pugh score 5 to 6.).
Treatment with Rosuvastatin/Ezetimibe KRKA is not recommended in patients with moderate (Child Pugh score 7 to 9) or severe (Child Pugh score more than 9) liver dysfunction (see sections 4.4 and 5.2).

Rosuvastatin/Ezetimibe KRKA is contraindicated in patients with active liver disease (see section 4.3).

Race
Increased systemic exposure of rosuvastatin has been seen in Asian subjects (see sections 4.3, 4.4 and 5.2). The recommended start dose is rosuvastatin 5 mg for patients of Asian ancestry. The 40 mg/10 mg dose is contraindicated in these patients.

Genetic polymorphisms
Genotypes of SLCO1B1 (OATP1B1) c.521CC and ABCG2 (BCRP) c.421AA have been shown to be associated with an increase in rosuvastatin exposure. For patients known to have the c.521CC or c.421AA genotype, half of the usually recommended dose and a maximum once daily dose of 20 mg of rosuvastatin is recommended (see sections 4.4, 4.5 and 5.2).

Dosage in patients with predisposing factors to myopathy
The recommended start dose is rosuvastatin 5 mg in patients with predisposing factors to myopathy (see section 4.4). The 40 mg/10 mg dose is contraindicated in some of these patients (see section 4.3).

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, ticagrelor 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/Ezetimibe KRKA in children below 18 years have not been established.
Rosuvastatin/Ezetimibe KRKA is not recommended for use in patients aged below 18 years.

Method of administration
For oral use

Rosuvastatin/Ezetimibe KRKA should be taken each day once at the same time of the day with or without food.

4.3 Contraindications

Rosuvastatin/Ezetimibe KRKA is contraindicated:

- in patients with hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- in patients with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3 x the upper limit of normal (ULN).
- in patients with severe renal impairment (creatinine clearance <30 ml/min).
- in patients with myopathy.
- in patients receiving concomitant combination of sofosbuvir/velpatasvir/voxilaprevir (see section 4.5).
- in patients receiving concomitant ciclosporin.
- during pregnancy and breast feeding and in women of childbearing potential not using appropriate contraceptive measures. Rosuvastatin/Ezetimibe KRKA 40 mg/10 mg is contraindicated in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

- moderate renal impairment (creatinine clearance <60 ml/min)
- hypothyroidism
- personal or family history of hereditary muscular disorders
- previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate
- alcohol abuse
- situations where an increase in plasma levels may occur
- Asian patients
- concomitant use of fibrates(see sections 4.4, 4.5 and 5.2)

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 rosuvastatin 40 mg dose. An assessment of renal function should be considered during routine follow-up of patients treated with rosuvastatin dose of 40 mg.

Skeletal muscle effects
Effects of rosuvastatin 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.

In post-marketing experience with ezetimibe, cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin concomitantly with ezetimibe. However, rhabdomyolysis has been reported very rarely with ezetimibe monotherapy and very rarely with the addition of ezetimibe to other agents known to be associated with increased risk of rhabdomyolysis. If myopathy is suspected based on muscle symptoms or is confirmed by a creatine phosphokinase (CPK) level >10 times the ULN, ezetimibe, any statin, and any of these other agents that the patient is taking concomitantly should be immediately discontinued. All patients starting therapy with Rosuvastatin/Ezetimibe KRKA should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness (see section 4.8).

In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia (see section 4.8). Rosuvastatin/Ezetimibe KRKA should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported.

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/Ezetimibe KRKA, as with other products containing HMG-CoA reductase inhibitors, should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis. 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/Ezetimibe KRKA 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/Ezetimibe KRKA and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of Rosuvastatin/Ezetimibe KRKA with fibrates should be carefully weighed against the potential risks of such combinations. The 40 mg dose of rosuvastatin is contraindicated with concomitant use of a fibrate (see sections 4.5 and 4.8)

Rosuvastatin/Ezetimibe 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).

<u>Fusidic acid</u>
Rosuvastatin/Ezetimibe 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/Ezetimibe KRKA and fusidic acid should only be considered on a case by case basis and under close medical supervision.

<u>Liver effects</u>

As with other products with HMG-CoA reductase inhibitors, Rosuvastatin/Ezetimibe 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 treatment. Rosuvastatin/Ezetimibe KRKA should be discontinued or the dose reduced if the level of serum transaminases is greater than 3 times the upper limit of normal. The reporting rate for serious hepatic events (consisting mainly of increased hepatic transaminases) in post-marketing use is higher at rosuvastatin 40 mg dose.

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

In controlled co-administration trials in patients receiving ezetimibe with a statin, consecutive transaminase elevations (≥3 X the upper limit of normal [ULN]) have been observed. Liver function tests should be performed at initiation of therapy with Rosuvastatin/Ezetimibe KRKA (see section 4.8).

Race
Pharmacokinetic studies with rosuvastatin show an increase in exposure in Asian subjects compared with Caucasians (see sections 4.2, 4.3 and 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 certain 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/m^2, 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.

Fibrates
The safety and efficacy of ezetimibe administered with fibrates have not been established.
If cholelithiasis is suspected in a patient receiving Rosuvastatin/Ezetimibe KRKA and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued (see sections 4.5 and 4.8).

Anticoagulants
If Rosuvastatin/Ezetimibe KRKA is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalised Ratio (INR) should be appropriately monitored (see section 4.5).

Severe cutaneous adverse reactions
Severe cutaneous adverse reactions including Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS), which could be life-threatening or fatal, have been reported with rosuvastatin. At the time of prescription, patients should be advised of the signs and symptoms of severe skin reactions and be closely monitored. If signs and symptoms suggestive of this reaction appears, Rosuvastatin/Ezetimibe KRKA should be discontinued immediately and an alternative treatment should be considered.

If the patient has developed a serious reaction such as SJS or DRESS with the use of Rosuvastatin/Ezetimibe KRKA, treatment with Rosuvastatin/Ezetimibe KRKA must not be restarted in this patient at any time.
Excipients
Rosuvastatin/Ezetimibe KRKA contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Rosuvastatin/Ezetimibe KRKA contains less than 1 mmol sodium (23 mg) per dose that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated combinations:

Ciclosporin: Rosuvastatin/Ezetimibe KRKA is contraindicated in patients receiving concomitant ciclosporin (see section 4.3). 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). Concomitant administration did not affect plasma concentrations of ciclosporin.

In a study of eight post-renal transplant patients with creatinine clearance of more than 50 ml/min on a stable dose of ciclosporin, a single 10 mg dose of ezetimibe resulted in a 3.4-fold (range 2.3 to 7.9-fold) increase in the mean AUC for total ezetimibe compared to a healthy control population, receiving ezetimibe alone, from another study (n=17). In a different study, a renal transplant patient with severe renal impairment who was receiving ciclosporin and multiple other medications, demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls receiving ezetimibe alone. In a two-period crossover study in 12 healthy subjects, daily administration of 20 mg ezetimibe for 8 days with a single 100 mg dose of ciclosporin on Day 7 resulted in a mean 15% increase in ciclosporin AUC (range 10% decrease to 51% increase) compared to a single 100 mg dose of ciclosporin alone. A controlled study on the effect of co-administered ezetimibe on ciclosporin exposure in renal transplant patients has not been conducted.

Not recommended combinations:

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).

Ticagrelor: Ticagrelor inhibits the transporter BCRP, causing a 2.6-fold increase in rosuvastatin AUC, which may result in increased risk of myopathy. Consideration should be given to the benefits of prevention of major adverse cardiovascular events by use of rosuvastatin and the risks with increased rosuvastatin plasma concentrations.

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).

Fibrates: 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 and other fibrates increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone. The 40 mg/10 mg dose is contraindicated with concomitant use of a fibrate (see sections 4.3 and 4.4). These patients should also start with the 5 mg dose.

In patients receiving fenofibrate and ezetimibe, physicians should be aware of the possible risk of cholelithiasis and gallbladder disease (see sections 4.4 and 4.8).

If cholelithiasis is suspected in a patient receiving ezetimibe and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued (see section 4.8).

Concomitant fenofibrate or gemfibrozil administration modestly increased total ezetimibe concentrations (approximately 1.5- and 1.7-fold respectively). Co-administration of ezetimibe with other fibrates has not been studied.

Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In animal studies, ezetimibe sometimes increased cholesterol in the gallbladder bile, but not in all species (see section 5.3). A lithogenic risk associated with the therapeutic use of ezetimibe cannot be ruled out.

Fusidic Acid: Interaction studies with rosuvastatin and fusidic acid have not been conducted. 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**.

Other interactions:

Antacids: Concomitant antacid administration decreased the rate of absorption of ezetimibe but had no effect on the bioavailability of ezetimibe. This decreased rate of absorption is not considered clinically significant.

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. The clinical relevance of this interaction has not been studied.

Anticoagulants: Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time in a study of twelve healthy adult males. However, there have been post-marketing reports of increased International Normalised Ratio (INR) in patients who had ezetimibe added to warfarin or fluindione. If ezetimibe is added to warfarin, another coumarin anticoagulant, or fluindione, INR should be appropriately monitored (see section 4.4).

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.

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).

In preclinical studies, it has been shown that ezetimibe does not induce cytochrome P450 drug metabolising enzymes. No clinically significant pharmacokinetic interactions have been observed between ezetimibe and drugs known to be metabolised by cytochromes P450 1A2, 2D6, 2C8, 2C9, and 3A4, or N-acetyltransferase.

Colestyramine: Concomitant colestyramine administration decreased the mean area under the curve (AUC) of total ezetimibe (ezetimibe plus ezetimibe-glucuronide) approximately 55%. The incremental low density lipoprotein cholesterol (LDL-C) reduction due to adding ezetimibe to colestyramine may be lessened by this interaction (see section 4.2).

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

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.

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. Start with a 5 mg once daily dose of rosuvastatin if the expected increase in exposure (AUC) is approximately 2-fold or higher. 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).

If medicinal product is observed to increase rosuvastatin AUC less than 2-fold, the starting dose need not be decreased but caution should be taken if increasing the rosuvastatin dose above 20 mg.

Table 1. Effect of co-administered medicinal products on rosuvastatin exposure (AUC; in order of decreasing magnitude) from published clinical trials

2-fold or greater than 2-fold increase in AUC of rosuvastatin		
Interacting drug dose regimen	Rosuvastatin dose regimen	Change in rosuvastatin AUC*
Sofosbuvir/velpatasvir/voxilaprevir (400 mg-100 mg-100 mg) + Voxilaprevir (100 mg) once daily for 15 days	10 mg single dose	7.4-fold ↑
Ciclosporin 75 mg BID to 200 mg BID, 6 months	10 mg OD, 10 days	7.1-fold ↑
Darolutamide 600 mg BID, 5 days	5 mg, single dose	5.2-fold ↑
Regorafenib 160 mg, OD, 14 days	5 mg single dose	3.8-fold ↑
Atazanavir 300 mg/ritonavir 100 mg OD, 8 days	10 mg, single dose	3.1-fold ↑
Roxadustat 200 mg QOD	10 mg, single dose	2.9-fold ↑
Velpatasvir 100 mg OD	10 mg, single dose	2.7-fold ↑
Momelotinib 200 mg OD, 6 days	10 mg, single dose	2.7-fold ↑
Ticagrelor 90 mg BID, 2 days	10 mg, single dose	2.6-fold ↑
Ombitasvir 25 mg/paritaprevir 150 mg/ Ritonavir 100 mg OD/ dasabuvir 400 mg BID, 14 days	5 mg, single dose	2.6-fold ↑
Teriflunomide, Leflunomide	Not available	2.5-fold ↑
Grazoprevir 200 mg/elbasvir 50 mg OD, 11 days	10 mg, single dose	2.3-fold ↑
Glecaprevir 400 mg/pibrentasvir 120 mg OD, 7 days	5 mg OD, 7 days	2.2-fold ↑
Lopinavir 400 mg/ritonavir 100 mg BID, 17 days	20 mg OD, 7 days	2.1-fold ↑
Capmatinib 400mg BID	10 mg, single dose	2.1-fold ↑
Clopidogrel 300 mg loading, followed by 75 mg at 24 hours	20 mg, single dose	2-fold ↑
Tafamidis 61 mg BID on Days 1 & 2, followed by OD on Days 3 to 9	10 mg, single dose	2.0-fold ↑

Fostamatinib 100 mg twice daily	20 mg, single dose	2.0-fold ↑
Gemfibrozil 600 mg BID, 7 days	80 mg, single dose	1.9-fold ↑
Febuxostat 120 mg OD	10 mg, single dose	1.9-fold ↑

Less than 2-fold increase in AUC of rosuvastatin		
Interacting drug dose regimen	Rosuvastatin dose regimen	Change in rosuvastatin AUC*
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 ↑**
Decrease in AUC of rosuvastatin		
Interacting drug dose regimen	Rosuvastatin dose regimen	Change in rosuvastatin AUC*
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 "↑", decrease as "↓".
**Several interaction studies have been performed at different rosuvastatin dosages, the table shows the most significant ratio
AUC = area under curve; OD = once daily; BID = twice daily; TID = three times daily; QID = four times daily; QOD = every other day

The following medical product/combinations did not have a clinically significant effect on the AUC ratio of rosuvastatin at coadministration: aleglitazar 0.3 mg 7 days dosing; fenofibrate 67 mg 7 days TID dosing; fluconazole 200mg 11 days OD dosing; fosamprenavir 700 mg/ritonavir 100 mg 8 days BID dosing; ketoconazole 200 mg 7 days BID dosing; rifampin 450 mg 7 days OD dosing; silymarin 140 mg 5 days TID dosing.

In clinical interaction studies, ezetimibe had no effect on the pharmacokinetics of dapsone, dextromethorphan, digoxin, oral contraceptives (ethinyl estradiol and levonorgestrel), glipizide, tolbutamide, or midazolam, during co-administration. Cimetidine, co-administered with ezetimibe, had no effect on the bioavailability of ezetimibe.

Paediatric population: Interaction studies have only been performed in adults. The extent of interactions in the paediatric population is not known.

4.6 Fertility, pregnancy and lactation

Rosuvastatin/Ezetimibe KRKA is contraindicated during pregnancy and breast feeding (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.

No clinical data are available on the use of ezetimibe during pregnancy. Animal studies on the use of ezetimibe in monotherapy have shown no evidence of direct or indirect harmful effects on pregnancy, embryofoetal development, birth or postnatal development (see section 5.3).

Breast-feeding
Limited data from published case reports indicate that both rosuvastatin and ezetimibe are present in human milk in low amounts. Due to rosuvastatin's mechanism of action, there is a potential risk for adverse reactions in infants. Rosuvastatin/Ezetimibe KRKA is contraindicated during breast-feeding.

Fertility
No clinical trial data are available on the effects of ezetimibe on human fertility. Ezetimibe had no effect on the fertility of male or female rats, rosuvastatin at higher doses showed testicular toxicity in monkeys and dogs (see section 5.3).

4.7 Effects on ability to drive and use machines

Studies to determine the effect of rosuvastatin or ezetimibe on the ability to drive and use machines have not been conducted. However, when driving vehicles or operating machines, it should be taken into account that dizziness has been reported.

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)

Summary of the safety profile
The adverse reactions seen with rosuvastatin are generally mild and transient. In controlled clinical trials, less than 4% of rosuvastatin-treated patients were withdrawn due to adverse reactions.

Adverse reaction profile for rosuvastatin is based on data from clinical studies and extensive post-marketing experience. Adverse reactions for ezetimibe were observed in patients treated with ezetimibe (N=2396) and at a greater incidence than placebo (N=1159) or in patients treated with ezetimibe coadministered with a statin (N=11308) and at a greater incidence than statin administered alone (N=9361). Post-marketing adverse reactions for ezetimibe were derived from reports containing ezetimibe either administered alone or with a statin.

Tabulated list of adverse reactions

Table 2. Adverse reactions based on data from clinical studies and post-marketing experience

MedDRA System Organ Class	**Undesirable Effects**	**Frequency**		
		Rosuvastatin	**Ezetimibe**	
Blood and lymphatic system disorders	Thrombocytopenia	Rare	Not known	
Immune system disorders	Hypersensitivity reactions including angioedema	Rare		
	Hypersensitivity reactions including rash, urticaria and anaphylaxis	–	Not known	
Endocrine disorders	Diabetes mellitus[1]	Common	–	
Metabolism and Nutrition Disorders	Decreased appetite	–	Uncommon	
Psychiatric disorders	Depression	Not known	Not known	
Nervous system disorders	Headache	Common	Common	
	Dizziness	Common	Not known	
	Polyneuropathy	Very rare	–	
	Memory loss	Very rare	–	

	Peripheral neuropathy	Not known	–	
	Sleep disturbances (including insomnia and nightmares)	Not known	–	
	Myasthenia gravis	Not known	–	
	Paraesthesia	–	Uncommon	
Eye disorders	Ocular myasthenia	Not known	–	
Vascular Disorders	Hot flush, hypertension	–	Uncommon	
Respiratory, thoracic and mediastinal disorders	Cough	Not known	Uncommon	
	Dyspnoea	Not known	Not known	
Gastrointestinal disorders	Constipation	Common	Not known	
	Nausea	Common	Uncommon	
	Abdominal pain	Common	Common	
	Pancreatitis	Rare	Not known	
	Diarrhoea	Not known	Common	
	Dry mouth	–	Uncommon	
	Gastritis	–	Uncommon	
	Flatulence	–	Common	
	Dyspepsia, gastrooesophageal reflux disease	–	Uncommon	
Hepatobiliary disorders	Increased hepatic transaminases	Rare	–	
	Jaundice	Very rare	–	
	Hepatitis	Very rare	Not known	
	Cholelithiasis	–	Not known	
	Cholecystitis	–	Not known	
Skin and subcutaneous tissue disorders	Pruritis	Uncommon	Uncommon	
	Rash	Uncommon	Uncommon	
	Urticaria	Uncommon	Uncommon	
	Stevens-Johnson syndrome	Not known	–	
	Erythema multiforme	–	Not known	
	Drug reaction with eosinophilia and systemic symptoms (DRESS)	Not known	–	
Musculoskeletal and connective tissue disorders	Myalgia	Common	Common	
	Myopathy (including myositis)	Rare	Not known	
	Rhabdomyolysis	Rare	Not known	
	Arthralgia	Very rare	Uncommon	
	Immune-mediated necrotising myopathy	Not known	–	
	Tendon disorders, sometimes complicated by rupture	Not known	–	
	Back pain	–	Uncommon	
	Muscular weakness	–	Uncommon	
	Pain in extremity	–	Uncommon	
	Muscle spasms, neck pain	–	Uncommon	
	Lupus-like	Rare	–	

	syndrome			
	Muscle rupture	Rare	–	
Renal and urinary disorders	Haematuria	Very rare	–	
Reproductive system and breast disorders	Gynaecomastia	Very rare	–	
General disorders and administration site conditions	Asthenia	Common	Uncommon	
	Oedema	Not known	–	
	Oedema peripheral	–	Uncommon	
	Fatigue	–	Common	
	Chest pain, pain	–	Uncommon	
Investigations	ALT and/or AST increased	–	Common	
	Blood CPK increased, gamma-glutamyltransferase increased, liver function test abnormal	–	Uncommon	
[1] Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/l, BMI >30 kg/m^2, raised triglycerides, history of hypertension).				

As with other HMG-CoA reductase inhibitors, the incidence of adverse drug reactions with rosuvastatin 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.

Laboratory values

In controlled clinical monotherapy trials with ezetimibe, the incidence of clinically important elevations in serum transaminases

(ALT and/or AST ≥ 3 X ULN, consecutive) was similar between ezetimibe (0.5%) and placebo (0.3%). In co-administration trials, the incidence was 1.3% for patients treated with ezetimibe co-administered with a statin and 0.4% for patients treated with a statin alone. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment (see section 4.4).

In clinical trials with ezetimibe, CPK >10 X ULN was reported for 4 of 1674 (0.2%) patients administered ezetimibe alone vs 1 of 786 (0.1%) patients administered placebo, and for 1 of 917 (0.1%) patients co-administered ezetimibe and a statin vs 4 of 929 (0.4%) patients administered a statin alone. There was no excess of myopathy or rhabdomyolysis associated with ezetimibe compared with the relevant control arm (placebo or statin alone) (see section 4.4).

Paediatric population

Creatine kinase elevations >10xULN and muscle symptoms with rosuvastatin following exercise or increased physical activity were observed more frequently in a 52-week clinical trial of children and adolescents compared to adults (see section 4.4). In other respects, the safety profile of rosuvastatin was similar in children and adolescents compared to adults.

In a study with ezetimibe involving paediatric (6 to 10 years of age) patients with heterozygous familial or non-familial hypercholesterolaemia (n = 138), elevations of ALT and/or AST (≥ 3X ULN, consecutive) were observed in 1.1% (1 patient) of the ezetimibe patients compared to 0% in the placebo group. There were no elevations of CPK (≥ 10X ULN). No cases of myopathy were reported.

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, Website: www.hpra.ie.

4.9 Overdose

In the event of an overdose, symptomatic and supportive measures should be employed.

Rosuvastatin
Liver function and CK levels should be monitored. Haemodialysis is unlikely to be of benefit.

Ezetimibe
In clinical studies, administration of ezetimibe, 50 mg/day, to 15 healthy subjects for up to 14 days, or 40 mg/day to 18 patients with primary hypercholesterolaemia for up to 56 days, was generally well tolerated. In animals, no toxicity was observed after single oral doses of 5,000 mg/kg of ezetimibe in rats and mice and 3,000 mg/kg in dogs.

A few cases of overdose with ezetimibe have been reported. Most have not been associated with adverse experiences. Reported adverse experiences have not been serious.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: lipid modifying agents; Combinations of various lipid modifying agents, ATC code: C10BA06.

Rosuvastatin

Mechanism of action
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.

Pharmacodynamic effects
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 (see Table 3). Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios.

Table 3: Dose response in patients with primary hypercholesterolaemia (type IIa and IIb) (adjusted mean percent change from baseline)

Dose	N	LDL-C	Total-C	HDL-C	TG	nonHDL-C	ApoB	ApoA-I
Placebo	13	-7	-5	3	-3	-7	-3	0
5	17	-45	-33	13	-35	-44	-38	4
10	17	-52	-36	14	-10	-48	-42	4
20	17	-55	-40	8	-23	-51	-46	5
40	18	-63	-46	10	-28	-60	-54	0

A therapeutic effect is obtained within 1 week following treatment initiation and 90% of maximum response is achieved in 2 weeks. The maximum response is usually achieved by 4 weeks and is maintained after that.

Clinical efficacy and safety
Rosuvastatin is effective in adults with hypercholesterolaemia, with and without hypertriglyceridaemia, regardless of race, sex, or age and in special populations such as diabetics, or patients with familial hypercholesterolaemia.

From pooled phase III data, rosuvastatin has been shown to be effective at treating the majority of patients with type IIa and IIb hypercholesterolaemia (mean baseline LDL-C about 4.8 mmol/l) to recognised European Atherosclerosis Society (EAS; 1998) guideline targets; about 80% of patients treated with 10 mg reached the EAS targets for LDL-C levels (< 3 mmol/l).

In a large study, 435 patients with heterozygous familial hypercholesterolaemia were given rosuvastatin from 20 mg to 80 mg in a force-titration design. All doses showed a beneficial effect on lipid parameters and treatment to target goals. Following titration to a daily dose of 40 mg (12 weeks of treatment), LDL-C was reduced by 53%. Thirty three percent (33%) of patients reached EAS guidelines for LDL-C levels (< 3 mmol/l).

In a force-titration, open label trial, 42 patients with homozygous familial hypercholesterolaemia were evaluated for their response to rosuvastatin 20-40 mg. In the overall population, the mean LDL-C reduction was 22%.

Ezetimibe

Mechanism of action
Ezetimibe is in a new class of lipid-lowering compounds that selectively inhibit the intestinal absorption of cholesterol and related plant sterols. Ezetimibe is orally active, and has a mechanism of action that differs from other classes of cholesterol-reducing compounds (e.g. statins, bile acid sequestrants [resins], fibric acid derivatives, and plant stanols). The molecular target of ezetimibe is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is responsible for the intestinal uptake of cholesterol and phytosterols.

Ezetimibe localises at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver; statins reduce cholesterol synthesis in the liver and together these distinct mechanisms provide complementary cholesterol reduction. In a 2-week clinical study in 18 hypercholesterolemic patients, ezetimibe inhibited intestinal cholesterol absorption by 54%, compared with placebo.

Pharmacodynamic effects

A series of preclinical studies was performed to determine the selectivity of ezetimibe for inhibiting cholesterol absorption. Ezetimibe inhibited the absorption of [14C]-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethinyl estradiol, or fat soluble vitamins A and D.

Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C.

Administration of ezetimibe with a statin is effective in reducing the risk of cardiovascular events in patients with coronary heart disease and ACS event history.

Clinical efficacy and safety

In controlled clinical studies, ezetimibe, either as monotherapy or co-administered with a statin significantly reduced total cholesterol (total-C), LDL-C, apolipoprotein B (Apo B), and triglycerides (TG) and increased HDL-C in patients with hypercholesterolaemia.

Primary hypercholesterolaemia

In a double-blind, placebo-controlled, 8-week study, 769 patients with hypercholesterolaemia already receiving statin monotherapy and not at National Cholesterol Education Program (NCEP) LDL-C goal (2.6 to 4.1 mmol/l [100 to 160 mg/dl], depending on baseline characteristics) were randomised to receive either ezetimibe 10 mg or placebo in addition to their on-going statin therapy.

Among statin-treated patients not at LDL-C goal at baseline (~82%), significantly more patients randomised to ezetimibe achieved their LDL-C goal at study endpoint compared to patients randomised to placebo, 72% and 19% respectively. The corresponding LDL-C reductions were significantly different (25% and 4% for ezetimibe versus placebo, respectively). In addition, ezetimibe, added to on-going statin therapy, significantly decreased total-C, Apo B, TG and increased HDL-C, compared with placebo. Ezetimibe or placebo added to statin therapy reduced median C-reactive protein by 10% or 0% from baseline, respectively.

In two, double-blind, randomised placebo-controlled, 12-week studies in 1.719 patients with primary hypercholesterolaemia, ezetimibe 10 mg significantly lowered total-C (13%), LDL-C (19%), Apo B (14%), and TG (8%) and increased HDL-C (3%) compared to placebo. In addition, ezetimibe had no effect on the plasma concentrations of the fat-soluble vitamins A, D, and E, no effect on prothrombin time, and, like other lipid-lowering agents, did not impair adrenocortical steroid hormone production.

Rosuvastatin/Ezetimibe

Clinical efficacy and safety

A 6-week, randomized, double-blind, parallel-group, clinical trial which evaluated the safety and efficacy of ezetimibe 10 mg added to stable rosuvastatin therapy versus up-titration of rosuvastatin from 5 to 10 mg or from 10 to 20 mg (n=440). Pooled data demonstrated that ezetimibe added to stable rosuvastatin 5 mg or 10 mg reduced LDL cholesterol by 21%. In contrast, doubling rosuvastatin to 10 mg or 20 mg reduced LDL cholesterol by 5.7% (between-group difference of 15.2%, p <0.001). Individually, ezetimibe plus rosuvastatin 5 mg reduced LDL cholesterol more than did rosuvastatin 10 mg (12.3% difference, p <0.001), and ezetimibe plus rosuvastatin 10 mg reduced LDL cholesterol more than did rosuvastatin 20 mg (17.5% difference, p <0.001).

A 6-week, randomized study was conducted to investigate the efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe 10 mg in patients at high risk of coronary heart disease (n=469). Significantly more patients receiving rosuvastatin/ezetimibe than rosuvastatin alone achieved their ATP III LDL cholesterol goal (<2.6 mmol/l [<100 mg/dl], 94.0% vs 79.1%, p <0.001) and the optional LDL cholesterol goal (<1.8 mmol/l [<70 mg/dl]) for very high-risk patients (79.6% vs 35.0%, p <0.001). The combination of rosuvastatin/ezetimibe reduced LDL cholesterol significantly more than rosuvastatin (-69.8% vs -57.1%, p <0.001). Other components of the lipid/lipoprotein profile were also significantly (p <0.001) improved with rosuvastatin/ezetimibe.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Rosuvastatin/Ezetimibe KRKA in all subsets of the paediatric population in the treatment of elevated cholesterol (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Rosuvastatin

Absorption
Maximum rosuvastatin plasma concentrations are achieved approximately 5 hours after oral administration. The absolute bioavailability is approximately 20%.

Distribution
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.

Biotransformation
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 N-desmethyl metabolite is approximately 50% less active than rosuvastatin whereas the lactone form is considered clinically inactive. Rosuvastatin accounts for greater than 90% of the circulating HMG-CoA reductase inhibitor activity.

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

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

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 (see "Paediatric population" below).

Race
Pharmacokinetic studies show an approximate 2-fold elevation in median AUC and C_{max} 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.

Genetic polymorphisms
Disposition of HMG-CoA reductase inhibitors, including rosuvastatin, involves OATP1B1 and BCRP transporter proteins coded by SLCO1B1 gene (OATP1B1) and ABCG2 gene (BCRP). Certain variants of these genes, like SLCO1B1 c.521CC and ABCG2 c.421AA are associated with an approximate 1.6-fold-higher rosuvastatin exposure (AUC) or 2.4-fold higher exposure, respectively, compared to the SLCO1B1 c.521TT or ABCG2 c.421CC genotypes. For patients who are known to have these genotypes (SLCO1B1 c.521CC or ABCG2 c.421AA), a lower daily dose of rosuvastatin is recommended

Paediatric population
Two pharmacokinetic studies with rosuvastatin (given as tablets) in paediatric patients with heterozygous familial hypercholesterolaemia 10 to 17 or 6 to 17 years of age (total of 214 patients) demonstrated that exposure in paediatric patients appears comparable to or lower than that in adult patients. Rosuvastatin exposure was predictable with respect to dose and time over a 2-year period.

Ezetimibe

Absorption
After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). Mean maximum plasma concentrations (C_{max}) occur within 1 to 2 hours for ezetimibe-glucuronide and 4 to 12 hours for ezetimibe. The absolute bioavailability of ezetimibe cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection.

Concomitant food administration (high fat or non-fat meals) had no effect on the oral bioavailability of ezetimibe when administered as ezetimibe 10-mg tablets. Ezetimibe can be administered with or without food.

Distribution
Ezetimibe and ezetimibe-glucuronide are bound 99.7 % and 88 to 92 % to human plasma proteins, respectively.

Biotransformation
Ezetimibe is metabolised primarily in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary excretion. Minimal oxidative metabolism (a phase I reaction) has been observed in all species evaluated. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20 % and 80 to 90 % of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with evidence of significant enterohepatic recycling. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours.

Elimination
Following oral administration of ^{14}C-ezetimibe (20 mg) to human subjects, total ezetimibe accounted for approximately 93 % of the total radioactivity in plasma. Approximately 78 % and 11 % of the administered radioactivity were recovered in the faeces and urine, respectively, over a 10-day collection period. After 48 hours, there were no detectable levels of radioactivity in the plasma.

Special populations:

Paediatric population
The pharmacokinetics of ezetimibe are similar between children ≥6 years and adults. Pharmacokinetic data in the paediatric population < 6 years of age are not available. Clinical experience in paediatric and adolescent patients includes patients with HoFH, HeFH, or sitosterolaemia.

Elderly
Plasma concentrations for total ezetimibe are about 2-fold higher in the elderly (≥ 65 years) than in the young (18 to 45 years). LDL-C reduction and safety profile are comparable between elderly and young subjects treated with ezetimibe. Therefore, no dosage adjustment is necessary in the elderly.

Hepatic impairment
After a single 10-mg dose of ezetimibe, the mean AUC for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic impairment (Child-Pugh score 5 or 6), compared to healthy subjects. In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic impairment (Child-Pugh score 7 to 9), the mean AUC for total ezetimibe was increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. No dosage adjustment is necessary for patients with mild hepatic impairment. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child-Pugh score > 9) hepatic impairment, ezetimibe is not recommended in these patients (see section 4.4).

Renal impairment
After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl ≤ 30 ml/min/1.73 m^2), the mean AUC for total ezetimibe was increased approximately 1.5-fold, compared to healthy subjects (n=9). This result is not considered clinically significant. No dosage adjustment is necessary for renally impaired patients.

An additional patient in this study (post-renal transplant and receiving multiple medications, including ciclosporin) had a 12-fold greater exposure to total ezetimibe.

Gender
Plasma concentrations for total ezetimibe are slightly higher (approximately 20 %) in women than in men. LDL-C reduction and safety profile are comparable between men and women treated with ezetimibe. Therefore, no dosage adjustment is necessary on the basis of gender.

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.

Ezetimibe

Animal studies on the chronic toxicity of ezetimibe identified no target organs for toxic effects. In dogs treated for four weeks with ezetimibe (≥ 0.03 mg/kg/day) the cholesterol concentration in the cystic bile was increased by a factor of 2.5 to 3.5. However, in a one-year study on dogs given doses of up to 300 mg/kg/day no increased incidence of cholelithiasis or other hepatobiliary effects were observed. The significance of these data for humans is not known. A lithogenic risk associated with the therapeutic use of ezetimibe cannot be ruled out.

In co-administration studies with ezetimibe and statins the toxic effects observed were essentially those typically associated with statins. Some of the toxic effects were more pronounced than observed during treatment with statins alone. This is attributed to pharmacokinetic and pharmacodynamic interactions in co-administration therapy. No such interactions occurred in the clinical studies. Myopathies occurred in rats only after exposure to doses that were several times higher than the human therapeutic dose (approximately 20 times the AUC level for statins and 500 to 2000 times the AUC level for the active metabolites).

In a series of in vivo and in vitro assays ezetimibe, given alone or co-administered with statins, exhibited no genotoxic potential. Long-term carcinogenicity tests on ezetimibe were negative.

Ezetimibe had no effect on the fertility of male or female rats, nor was it found to be teratogenic in rats or rabbits, nor did it affect prenatal or postnatal development. Ezetimibe crossed the placental barrier in pregnant rats and rabbits given multiple doses of 1000 mg/kg/day. The co-administration of ezetimibe and statins was not teratogenic in rats. In pregnant rabbits a small number of skeletal deformities (fused thoracic and caudal vertebrae, reduced number of caudal vertebrae) were observed. The co-administration of ezetimibe with lovastatin resulted in embryolethal effects.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Microcrystalline cellulose (E460)
Lactose
Mannitol (E421)
Crospovidone type A
Croscarmellose sodium
Magnesium stearate (E470b)
Povidone K30
Sodium laurilsulfate (E487)
Colloidal anhydrous silica (E551)

Film coating:
Lactose monohydrate
Hypromellose (E464)
Titanium dioxide (E171)
Triacetin
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

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, 30, 40, 90 and 100 film-coated tablets, in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA1347/108/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

February 2026