1. NAME OF THE MEDICINAL PRODUCT

Roxera® 5 mg film-coated tablets
Roxera® 10 mg film-coated tablets
Roxera® 20 mg film-coated tablets
Roxera® 40 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5 mg rosuvastatin (as rosuvastatin calcium).
Each film-coated tablet contains 10 mg rosuvastatin (as rosuvastatin calcium).
Each film-coated tablet contains 20 mg rosuvastatin (as rosuvastatin calcium).
Each film-coated tablet contains 40 mg rosuvastatin (as rosuvastatin calcium).

Excipient:

	5 mg	10 mg	20 mg	40 mg
Lactose	40 mg	40 mg	80 mg	160 mg

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

5 mg: White, round, slightly biconvex, film-coated tablets with bevelled edges and with engraved number 5 on one side.
10 mg: White, round, slightly biconvex, film-coated tablets with bevelled edges and with engraved number 10 on one side.
20 mg: White, round, film-coated tablets with bevel edge.
40 mg: White, biconvex, film-coated capsule shape tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of hypercholesterolaemia

Adults, adolescents and children aged 10 years or older with 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.

Prevention of Cardiovascular Events

Prevention of major cardiovascular events in patients who are estimated to have a high risk for a first cardiovascular event (see Section 5.1), as an adjunct to correction of other risk factors.

4.2 Posology and method of administration

Before treatment initiation the patient should be placed on a standard cholesterol-lowering diet that should continue during treatment. The dose should be individualised according to the goal of therapy and patient response, using current consensus guidelines.

Roxera may be given at any time of day, with or without food.

Treatment of hypercholesterolaemia

The recommended start dose is 5 mg or 10 mg orally once daily in both statin naïve or patients switched from another HMG CoA reductase inhibitor. The choice of start dose should take into account the individual patient's cholesterol level and future cardiovascular risk as well as the potential risk for adverse reactions (see below). A dose adjustment to the next dose level can be made after 4 weeks, if necessary (see Section 5.1). In light of the increased reporting rate of adverse reactions with the 40 mg dose compared to lower doses (see Section 4.8), a final titration to the maximum dose of 40 mg should only be considered in patients with severe hypercholesterolaemia at high cardiovascular risk (in particular those with familial hypercholesterolaemia), who do not achieve their treatment goal on 20 mg, and in whom routine follow-up will be performed (see Section 4.4). Specialist supervision is recommended when the 40 mg dose is initiated.

Prevention of cardiovascular events

In the cardiovascular events risk reduction study, the dose used was 20 mg daily (see Section 5.1).

Paediatric population

Paediatric use should only be carried out by specialists.

Children and adolescents 10 to 17 years of age (boys Tanner Stage II and above, and girls who are at least 1 year post-menarche)
In children and adolescents with heterozygous familial hypercholesterolaemia the usual start dose is 5 mg daily. The usual dose range is 5-20 mg orally once daily. Titration should be conducted according to the individual response and tolerability in paediatric patients, as recommended by the paediatric treatment recommendations (see Section 4.4). Children and adolescents should be placed on standard cholesterol-lowering diet before rosuvastatin treatment initiation; this diet should be continued during rosuvastatin treatment. Safety and efficacy of doses greater than 20 mg have not been studied in this population.
The 40 mg tablet is not suitable for use in paediatric patients.

Children younger than 10 years
Experience in children younger than 10 years is limited to a small number of children (aged between 8 and 10 years) with homozygous familial hypercholesterolaemia. Therefore, Roxera is not recommended for use in children younger than 10 years.

Use in the elderly

A start dose of 5 mg is recommended in patients older than 70 years (see Section 4.4). No other dose adjustment is necessary in relation to age.

Dosage in patients with renal insufficiency

No dose adjustment is necessary in patients with mild to moderate renal impairment. The recommended start dose is 5 mg in patients with moderate renal impairment (creatinine clearance of less than 60 ml/min). The 40 mg dose is contraindicated in patients with moderate renal impairment. The use of Roxera in patients with severe renal impairment is contraindicated for all doses (See Section 4.3 and Section 5.2).

Dosage in patients with 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. Roxera is contraindicated in patients with active liver disease (see Section 4.3).

Race

Increased systemic exposure has been seen in Asian subjects (see Section 4.4 and Section 5.2). The recommended start dose is 5 mg for patients of Asian ancestry. The 40 mg dose is contraindicated in these patients.

Dosage in patients with pre-disposing factors to myopathy

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

4.3 Contraindications

Roxera is contraindicated:
- in patients with hypersensitivity to rosuvastatin or to any of the excipients.
- 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 less than 30 ml/min).
- in patients with myopathy.
- in patients receiving concomitant ciclosporin.
- during pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures.

The 40 mg dose is contraindicated in patients with pre-disposing factors for myopathy/ rhabdomyolysis. Such factors include:
- moderate renal impairment (creatinine clearance less than 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 the 40 mg dose. An assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40 mg.

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 higher than 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.
As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis associated with rosuvastatin in post-marketing use is higher at the 40 mg dose.

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 (more than five times above ULN) a confirmatory test should be carried out within 5–7 days. If the repeat test confirms a baseline CK of more than five times above ULN, treatment should not be started.

Before treatment
Roxera, as with other 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 more than 70 years;
- situations where an increase in plasma levels of rosuvastatin may occur (see Section 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 (more than five times above ULN) 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 (more than five times above ULN) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are equal or less than five times ULN). If symptoms resolve and CK levels return to normal, then consideration should be given to re-introducing Roxera or an alternative HMGCoA reductase inhibitor at the lowest dose with close monitoring. Routine monitoring of CK levels in asymptomatic patients is not warranted.
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 Roxera and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of Roxera with fibrates or niacin should be carefully weighed against the potential risks of such combinations. The 40 mg dose is contraindicated with concomitant use of a fibrate (see Section 4.5 and Section 4.8).
Roxera 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 inhibitors, Roxera 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. Roxera 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 the 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 Roxera.

Protease inhibitors
The concomitant use with protease inhibitors is not recommended (see Section 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 a patient has developed interstitial lung disease, statin therapy should be discontinued.

Diabetes mellitus
In patients with fasting glucose 5.6 to 6.9 mmol/L, treatment with rosuvastatin has been associated with an increased risk of diabetes mellitus (see Section 4.8).

Lactose intolerance
Roxera film-coated tablets contain 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 interaction

Ciclosporin
During concomitant treatment with rosuvastatin and ciclosporin, rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers (see Section 4.3).
Concomitant administration did not affect plasma concentrations of ciclosporin.

Vitamin K antagonists
As with other HMG-CoA reductase inhibitors, the initiation of treatment or dosage up-titration of Roxera 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 downtitration of Roxera may result in a decrease in INR. In such situations, appropriate monitoring of INR is desirable.

Ezetimibe
Concomitant use of rosuvastatin and ezetimibe resulted in no change to AUC or C_{max} for either drug. However, a pharmacodynamic interaction, in terms of adverse effects, between Roxera and ezetimibe cannot be ruled out (see Section 4.4).

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 (higher 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. The 40 mg dose is contraindicated with concomitant use of a fibrate (see Section 4.3 and Section 4.4). These patients should also start with the 5 mg dose.

Protease inhibitors
Although the exact mechanism of interaction is unknown, concomitant protease inhibitor use may strongly increase rosuvastatin exposure. In a pharmacokinetic study, co-administration of 20 mg rosuvastatin and a combination product of two protease inhibitors (400 mg lopinavir / 100 mg ritonavir) in healthy volunteers was associated with an approximately two-fold and five-fold increase in rosuvastatin steady-state $AUC_{(0-24)}$ and C_{max} respectively. Therefore, concomitant use of rosuvastatin in HIV patients receiving protease inhibitors is not recommended (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. The clinical relevance of this interaction has not been studied.

Erythromycin
Concomitant use of rosuvastatin and erythromycin resulted in a 20% decrease in $AUC_{(0-t)}$ and a 30% decrease in C_{max} of rosuvastatin. This interaction may be caused by the increase in gut motility caused by erythromycin.

Oral contraceptive/hormone replacement therapy (HRT)
Concomitant use of rosuvastatin and an oral contraceptive resulted in an increase in ethinyl oestradiol 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.

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.
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).
Concomitant administration of itraconazole (an inhibitor of CYP3A4) and rosuvastatin resulted in a

28% increase in AUC of rosuvastatin. This small increase is not considered clinically significant. Therefore, drug interactions resulting from cytochrome P450-mediated metabolism are not expected.

4.6 Pregnancy and lactation

Roxera is contraindicated in pregnancy and lactation.

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.

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

4.7 Effects on 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.

4.8 Undesirable effects

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

The frequencies of adverse events are ranked according to the following:
- 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)

Immune system disorders
Rare: hypersensitivity reactions including angioedema

Endocrine disorders
Common: diabetes mellitus[1]

Nervous system disorders
Common: headache, dizziness

Gastrointestinal disorders
Common: constipation, nausea, abdominal pain
Rare*:* pancreatitis

Skin and subcutaneous tissue disorders
Uncommon: pruritus, rash and urticaria

Musculoskeletal, connective tissue and bone disorders
Common: myalgia

Rare: myopathy and rhabdomyolysis

Renal and urinary disorders
Uncommon: proteinuria

General disorders
Common: asthenia

[1] Observed in the JUPITER study (reported overall frequency 2.8% in rosuvastatin and 2.3% in placebo) mostly in patients with fasting glucose 5.6 to 6.9 mmol/L.

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

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 less than 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 more than 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 (more than five times above ULN), 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.

Post Marketing Experience: In addition to the above, the following adverse events have been reported during post marketing experience for rosuvastatin:

Nervous system disorders
Very rare: polyneuropathy, memory loss

Gastrointestinal disorders
Not known: diarrhoea

Hepatobiliary disorders
Very rare: jaundice, hepatitis
Rare: increased transaminases

Skin and subcutaneous tissue disorders
Not known: Stevens-Johnson syndrome

Musculoskeletal disorders
Very rare: arthralgia

Renal disorders
Very rare: haematuria

General disorders and administration site conditions
Not known: oedema

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.

Paediatric population: Creatine kinase elevations more than ten times above ULN and muscle symptoms 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.

4.9 Overdose

There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Liver function and CK levels should be monitored. Haemodialysis is unlikely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG CoA reductase inhibitors, ATC code: C10AA07.

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 1). Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios.

Table 1 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

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 (less than 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%. 33% of patients reached EAS guidelines for LDL-C levels (less than 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%.

In clinical studies with a limited number of patients, rosuvastatin has been shown to have additive efficacy in lowering triglycerides when used in combination with fenofibrate and in increasing HDL-C levels when used in combination with niacin (see Section 4.4).

In a multi-centre, double-blind, placebo-controlled clinical study (METEOR), 984 patients between 45 and 70 years of age and at low risk for coronary heart disease (defined as Framingham risk less than 10% over 10 years), with a mean LDL-C of 4.0 mmol/l (154.5 mg/dL), but with subclinical atherosclerosis (detected by Carotid Intima Media Thickness) were randomised to 40 mg rosuvastatin once daily or placebo for 2 years. Rosuvastatin significantly slowed the rate of progression of the maximum CIMT for the 12 carotid artery sites compared to placebo by -0.0145 mm/year [95% confidence interval -0.0196, -0.0093; $p<0.0001$]. The change from baseline was -0.0014 mm/year (-0.12%/year (non-significant)) for rosuvastatin compared to a progression of +0.0131 mm/year (1.12%/year ($p<0.0001$)) for placebo. No direct correlation between CIMT decrease and reduction of the risk of cardiovascular events has yet been demonstrated. The population studied in METEOR is low risk for coronary heart disease and does not represent the target population of rosuvastatin 40 mg. The 40 mg dose should only be prescribed in patients with severe hypercholesterolaemia at high cardiovascular risk (see Section 4.2).

In the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study, the effect of rosuvastatin on the occurrence of major atherosclerotic cardiovascular disease events was assessed in 17,802 men (50 years or older) and women (60 years or older).

Study participants were randomly assigned to placebo (n=8901) or rosuvastatin 20 mg once daily (n=8901) and were followed for a mean duration of 2 years.

LDL-cholesterol concentration was reduced by 45% ($p<0.001$) in the rosuvastatin group compared to the placebo group.

In a post-hoc analysis of a high-risk subgroup of subjects with a baseline Framingham risk score more than 20% (1558 subjects) there was a significant reduction in the combined end-point of cardiovascular death, stroke and myocardial infarction (p=0.028) on rosuvastatin treatment versus placebo. The absolute risk reduction in the event rate per 1000 patient-years was 8.8. Total mortality was unchanged in this high risk group (p=0.193). In a post-hoc analysis of a high-risk subgroup of subjects (9302 subjects total) with a baseline SCORE risk 5% or more (extrapolated to include subjects above 65 yrs) there was a significant reduction in the combined end-point of cardiovascular death, stroke and myocardial infarction (p=0.0003) on rosuvastatin treatment versus placebo. The absolute risk reduction in the event rate was 5.1 per 1000 patient-years. Total mortality was unchanged in this high risk group (p=0.076).

In the JUPITER trial there were 6.6% of rosuvastatin and 6.2% of placebo subjects who discontinued use of study medication due to an adverse event. The most common adverse events that led to treatment discontinuation were: myalgia (0.3% rosuvastatin, 0.2% placebo), abdominal pain (0.03% rosuvastatin, 0.02% placebo) and rash (0.02% rosuvastatin, 0.03% placebo). The most common adverse events at a rate greater than or equal to placebo were urinary tract infection (8.7% rosuvastatin, 8.6% placebo), nasopharyngitis (7.6% rosuvastatin, 7.2% placebo), back pain (7.6% rosuvastatin, 6.9% placebo) and myalgia (7.6% rosuvastatin, 6.6% placebo).

Paediatric population

In a double-blind, randomized, multi-centre, placebo-controlled, 12-week study (n=176, 97 male and 79 female) followed by a 40-week (n=173, 96 male and 77 female), open-label, rosuvastatin dose-titration phase, patients 10-17 years of age (Tanner stage II-V, females at least 1 year post-menarche) with heterozygous familial hypercholesterolaemia received rosuvastatin 5, 10 or 20 mg or placebo daily for 12 weeks and then all received rosuvastatin daily for 40 weeks. At study entry, approximately 30% of the patients were 10–13 years and approximately 17%, 18%, 40%, and 25% were Tanner stage II, III, IV, and V, respectively.

LDL-C was reduced 38.3%, 44.6%, and 50.0% by rosuvastatin 5, 10 and 20 mg, respectively, compared to 0.7% for placebo.

At the end of the 40-week, open-label, titration to goal, dosing up to a maximum of 20 mg once daily, 70 of 173 patients (40.5%) had achieved the LDL-C goal of less than 2.8 mmol/l.

After 52 weeks of study treatment, no effect on growth, weight, BMI or sexual maturation was detected (see Section 4.4). The clinical trial experience in children and adolescent patients is limited and the long-term effects of rosuvastatin (older than 1 year) on puberty are unknown. This trial (n=176) was not suited for comparison of rare adverse drug events.

5.2 Pharmacokinetic properties

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.

Metabolism

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.

Excretion
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
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 insufficiency
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 less than 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 insufficiency
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.

Paediatric population
The pharmacokinetic parameters in paediatric patients with heterozygous familial hypercholesterolaemia aged 10 to 17 years have not been fully characterised. A small pharmacokinetic

study with rosuvastatin (given as tablets) in 18 paediatric patients demonstrated that exposure in paediatric patients appears comparable to exposure in adult patients. In addition, the results indicate that a large deviation from dose proportionality is not expected.

5.3 Preclinical safety data

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

Film coating:
Lactose monohydrate
Titanium dioxide (E171)
Macrogol 6000
Basic butylated methacrylate copolymer

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in original package in order to protect from light. No special temperature storage conditions are required.

6.5 Nature and contents of container

Blister pack (OPA/Al/PVC – Al): 28 and 84 tablets of 5 mg, 10 mg and 20 mg (2 and 6 blister packs of 14 tablets), in a box.

Blister pack (OPA/Al/PVC – Al): 28 and 84 tablets of 40 mg (4 and 12 blister packs of 7 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(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT