

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=0.07).

In the JUPITER trial, there were 46% of rosuvastatin and 52% 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 (0.02% rosuvastatin, 0.02% placebo) and rash (0.02% rosuvastatin, 0.02% placebo). The most common adverse events at a rate greater than or equal to placebo were urinary tract infection (8.7% rosuvastatin, 6.6% placebo), nasopharyngitis (7.6% rosuvastatin, 7.2% placebo), back pain (7.6% rosuvastatin, 6.9% placebo) and myalgia (7.6% rosuvastatin, 6.5% placebo).

#### Paediatric population

In a double-blind, randomised, multi-centre, placebo-controlled, 12-week study (n=178, 57 male and 79 female) followed by a 40-week (n=173, 96 male and 77 female), open-label, rosuvastatin-dose-escalation phase, patients 10 to 17 years of age (Tanner stage IV), females at least 1-year post-menarche with heterozygous familial hypercholesterolaemia received rosuvastatin 5, 10 or 20mg 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 to 13 years and approximately 17%, 18%, 40%, and 25% were Tanner stage I, II, IV, and V, respectively. LDL-C was reduced 38.3%, 44.6%, and 50.0% by rosuvastatin 5, 10 and 20mg, 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 20mg once daily, 70 of 173 patients (40.5%) had achieved the LDL-C goal of less than 2.6 mmol/L.

After 12 weeks of study treatment, no effect on growth, weight, BMI or sexual maturation was detected. This trial (n=178) was not suited for comparison of rare adverse drug events.

Rosuvastatin was also studied in a 2-year open-label, titration-to-goal study in 158 children with heterozygous familial hypercholesterolaemia aged 6 to 17 years (81 males and 110 females, Tanner stage IV-V). The starting dose for all patients was 5mg rosuvastatin once daily. Patients aged 6 to 9 years (n=64) could titrate to a maximum dose of 10mg once daily and patients aged 10 to 17 years (n=134) to a maximum dose of 20mg once daily.

After 24 months of treatment with rosuvastatin, the LS mean percent reduction from the baseline value in LDL-C was 42% (Baseline: 230mg/L, Month 24: 133 mg/L). For each age group, the LS mean percent reductions from baseline values in LDL-C were 43% (Baseline: 230mg/L, Month 24: 124mg/L), 40% (Baseline: 234mg/L, Month 24: 124 mg/L) and 39% (Baseline: 241mg/L, Month 24: 153mg/L) in the 6- to 10-, 10- to 14-, and 14- to 17 age groups, respectively.

Rosuvastatin 5mg, 10mg, and 20mg also achieved statistically significant mean changes from baseline for the following secondary lipid and lipoprotein variables: HDL-C, TG, non-HDL-C, LDL-C, HDL-C, HDL-C, HDL-C, non-HDL-C, HDL-C, ApoB, ApoB/ApoA1. These changes were each in the direction of improved lipid response and were sustained over 2 years.

No effect on growth, weight, BMI or sexual maturation was detected after 24 months of treatment. Rosuvastatin was studied in a randomised, double-blind, placebo-controlled, multi-centre, cross-over study with 20mg once daily versus placebo in 14 children and adolescents (aged from 6 to 17 years) with heterozygous familial hypercholesterolaemia. The study was divided into an active treatment phase during which patients were treated with rosuvastatin 10mg, a cross-over phase that consisted of a 6-week treatment period with rosuvastatin 20mg preceded or followed by a 6-week placebo treatment period, and a 12-week maintenance phase during which all patients were treated with rosuvastatin 20mg. Patients who entered the study on ezetimibe or apolipoprotein therapy continued the treatment throughout the entire study.

A statistically significant (p<0.003) reduction in LDL-C (22.9%, 85.4mg/L, or 2.2 mmol/L) was observed following 6 weeks of treatment with rosuvastatin 20mg versus placebo. Statistically significant reductions in Total-C (20.1%, p=0.003), non-HDL-C (22.9%, p=0.003) and ApoB (17.1%, p=0.024) were observed. Reductions were also seen in TG, LDL-C:HDL-C, Total-C:HDL-C, non-HDL-C:HDL-C and ApoB:HDL-C. Following 6 weeks of treatment with rosuvastatin 20mg versus placebo, the reduction in LDL-C after 6 weeks of treatment with rosuvastatin 20mg of treatment with placebo was maintained over 12 weeks of continuous therapy. One patient had a further reduction in LDL-C (8.0%), Total-C (6.7%) and non-HDL-C (7.4%) following 6 weeks of treatment with 40mg after up-titration.

During an extended open-label treatment of 8 of these patients with 20mg rosuvastatin for up to 90 weeks, the LDL-C reduction was maintained in the area of -12.1% to -21.2%. In the 7 available children and adolescent patients (aged from 8 to 17 years) from the cross-over open label study with heterozygous familial hypercholesterolaemia, the percent reduction in LDL-C (21.9%), Total-C (19.2%) and non-HDL-C (21.0%) from baseline following 6 weeks of treatment with rosuvastatin 20mg was consistent with that observed in the aforementioned study in children and adolescents with heterozygous familial hypercholesterolaemia.

#### PHARMACOKINETIC

**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 in plasma 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. CYP2C8 was the principal isoenzyme involved, with CYP11A and CYP2C9 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 3% 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 l/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 exposure in children and adolescents with heterozygous familial hypercholesterolaemia appears to be similar to or lower than in adult patients with dyslipidaemia.

**Race:** Pharmacokinetic studies show an approximate 2-fold elevation in median AUC and  $C_{max}$  in Asian subjects (Japanese, Chinese, Filipino, Vietnamese and Korean) compared with Caucasian, African, Indian and South American subjects. The increase in AUC and  $C_{max}$  is not statistically significant. 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 (GFR <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.

**Genetic polymorphisms:** Disposition of HMG-CoA reductase inhibitors, including rosuvastatin, involves OATP1B1 and BCRP transporter proteins. In patients with SLC01B1 (OATP1B1) and/or ABCG2 (BCRP) genetic polymorphisms there is a risk of increased rosuvastatin exposure. Individual polymorphisms of SLC01B1 c5512G and ABCG2 c4214A are associated with a higher rosuvastatin exposure (AUC) compared to the SLC01B1 c3871T or ABCG2 c4212C genotypes. This specific genotyping is not established in clinical practice, but for patients who are known to have these types of polymorphisms, 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.

#### 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 in 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.

#### LIST OF EXCIPIENTS

**Rosuvastatin Calcium Tablets 5mg:** Microcrystalline Cellulose, Lactose Monohydrate, Magnesium, Croscarmellose, Magnesium Stearate, Opadry II 33K50203 Yellow (Tartaric Acid, Titanium Dioxide, Sunset Yellow FCF Aluminium Lake, Indigo Carmine Aluminium Lake, Titanium Dioxide, Hydroxyethylcellulose, Lactose Monohydrate, Triacetin).

**Rosuvastatin Calcium Tablets 10mg:** Microcrystalline Cellulose, Lactose Monohydrate, Magnesium, Croscarmellose, Magnesium Stearate, Opadry II 33K54005 Pink (Titanium Dioxide, Sunset Yellow FCF Aluminium Lake, Allura Red AC Aluminium Lake, Indigo Carmine Aluminium Lake, Hydroxyethylcellulose, Lactose Monohydrate, Triacetin).

**Rosuvastatin Calcium Tablets 20mg:** Microcrystalline Cellulose, Lactose Monohydrate, Magnesium, Croscarmellose, Magnesium Stearate, Opadry II 33K54005 Pink (Titanium Dioxide, Sunset Yellow FCF Aluminium Lake, Allura Red AC Aluminium Lake, Indigo Carmine Aluminium Lake, Hydroxyethylcellulose, Lactose Monohydrate, Triacetin).

#### PRESENTATION

Blister Pack of 10's

#### STORAGE INSTRUCTIONS

STORE UP TO 30°C  
PROTECT FROM MOISTURE  
KEEP OUT OF REACH OF CHILDREN

#### Zydus

**Cadila**  
Manufactured by  
Cadila Healthcare Limited  
Kuntam Industrial Estate,  
Plot No. 202-213, Kundam,  
Coat - 603 115, INDIA.

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

#### ZYROVA

#### Rosuvastatin Calcium Tablets

#### COMPOSITION

**ZYROVA 5**  
Rosuvastatin Calcium Tablets 5mg  
Each film coated tablet contains:  
Rosuvastatin Calcium Ph. Eur.  
Equivalent to Rosuvastatin 5mg  
Colours: Titanium Dioxide, Tartrazine Aluminium Lake, Allura Red AC Aluminium Lake, Indigo Carmine Aluminium Lake

#### ZYROVA 10

Rosuvastatin Calcium Tablets 10mg  
Each film coated tablet contains:  
Rosuvastatin Calcium Ph. Eur.  
Equivalent to Rosuvastatin 10mg  
Colours: Titanium Dioxide, Sunset Yellow FCF Aluminium Lake, Allura Red AC Aluminium Lake, Indigo Carmine Aluminium Lake

#### ZYROVA 20

Rosuvastatin Calcium Tablets 20mg  
Each film coated tablet contains:  
Rosuvastatin Calcium Ph. Eur.  
Equivalent to Rosuvastatin 20mg  
Colours: Titanium Dioxide, Sunset Yellow FCF Aluminium Lake, Allura Red AC Aluminium Lake, Indigo Carmine Aluminium Lake

#### DESCRIPTION

**Rosuvastatin Calcium Tablets 5mg:** Yellow colored, round shaped, biconvex beveled edge film coated tablets, plain on both sides.  
**Rosuvastatin Calcium Tablets 10mg:** Pink colored, round shaped, biconvex beveled edge film coated tablets, plain on both sides.  
**Rosuvastatin Calcium Tablets 20mg:** Pink colored, round shaped, biconvex beveled edge film coated tablets, plain on both sides.

#### THERAPEUTIC INDICATIONS

**Treatment of Hypercholesterolemia**  
Adults, adolescents and children aged 6 years or older with primary hypercholesterolemia (type I) including heterozygous familial hypercholesterolemia) or mixed dyslipidemia (type IIb) as an adjunct to diet when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate. Adults, adolescents and children aged 6 years or older with homozygous familial hypercholesterolemia 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, as an adjunct to correction of other risk factors.

**POPOLOGY 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 individualized according to the goal of therapy and patient response, using current consensus guidelines. Rosuvastatin may be given at any time of day, with or without food.

**Treatment of hypercholesterolemia**  
The recommended start dose is 5 or 10mg orally once daily in both statin naive 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. A dose adjustment to the next dose level can be made after 4 weeks, if necessary. In light of the increased starting rate of adverse reactions with the 40mg dose compared to lower doses, a first titration to the maximum dose of 40mg should only be considered in patients with severe hypercholesterolemia at high cardiovascular risk (in particular those with familial hypercholesterolemia), who do not achieve their treatment goal on 20mg, and when other follow-up will be performed. Speeded escalation is recommended when the 40mg dose is initiated.

**Prevention of cardiovascular events**  
In the cardiovascular events risk reduction study, the dose used was 20mg daily.

**Paediatric population**  
Paediatric use should only be carried out by specialists.  
Children and adolescents (6 to 17 years of age) (Phase 3a/IIc)  
**Heterozygous familial hypercholesterolemia**  
In children and adolescents with heterozygous familial hypercholesterolemia the usual start dose is 5mg daily.

• In children 6 to 9 years of age with heterozygous familial hypercholesterolemia, the usual dose range is 5mg orally once daily. Safety and efficacy of doses greater than 10mg have not been studied in this population.  
• In children 10 to 17 years of age with heterozygous familial hypercholesterolemia, the usual dose range is 5-20mg orally once daily. Safety and efficacy of doses greater than 20mg have not been studied in this population.

Titration should be conducted according to the individual response and tolerability in paediatric patients, as recommended by the paediatric treatment recommendations. Children and adolescents should be placed on standard cholesterol-lowering diet before rosuvastatin treatment; this diet should be continued during rosuvastatin treatment.

**Homozygous familial hypercholesterolemia**  
In children 6 to 17 years of age with homozygous familial hypercholesterolemia, the recommended maximum dose is 20mg once daily.  
A starting dose of 5 to 10mg once daily depending on age, weight and prior statin use is advised. Titration to the maximum dose of 20mg once daily should be conducted according to the individual response and tolerability in paediatric patients, as recommended by the paediatric treatment recommendations. Children and adolescents should be placed on standard cholesterol-lowering diet before rosuvastatin treatment; this diet should be continued during rosuvastatin treatment.

There is limited experience with doses other than 20mg in this population.  
The 40mg tablet is not suitable for use in paediatric patients.  
**Older younger than 18 years**  
The safety/efficacy of use in children younger than 6 years has not been studied. Therefore, Rosuvastatin is not recommended for use in children younger than 6 years.

**Use in the elderly**  
A start dose of 5mg is recommended in patients >70 years. 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 5mg in patients with moderate renal impairment (creatinine clearance <60 ml/min). The 40mg dose is contraindicated in patients with moderate renal impairment. The use of Rosuvastatin in patients with severe renal impairment is contraindicated for all doses.

**Dosage in patients with hepatic impairment**  
There is no increase in systemic exposure to rosuvastatin in subjects with Child-Pugh scores of 7 and 9. However, increased systemic exposure has been observed in subjects with Child-Pugh scores of 8 and 9. In these patients an assessment of renal function should be considered. There is no experience in subjects with Child-Pugh scores above 9. Rosuvastatin is contraindicated in patients with active liver disease.

**Race**  
Increased systemic exposure has been seen in Asian subjects. The recommended start dose is 5mg for patients of Asian ancestry. The 40mg dose is contraindicated in these patients.  
**Genetic polymorphisms**  
Specific types of genetic polymorphisms are known that can lead to increased rosuvastatin exposure. For patients who are known to have such specific types of polymorphisms, a lower daily dose of Rosuvastatin is recommended.

**Dosage in patients with pre-disposing factors to myopathy**  
The recommended start dose is 5mg in patients with predisposing factors to myopathy. The 40mg dose is contraindicated in some of these patients.  
**Concomitant therapy**  
Rosuvastatin is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when Rosuvastatin is administered concomitantly with certain medicinal products that may increase the plasma concentration of rosuvastatin due to interactions with these transporter proteins (e.g. ciclosporin and certain protease inhibitors including combinations of ritonavir with abacavir, lopinavir and/or tipranavir). 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/benefit ratio and Rosuvastatin dosing adjustments should be carefully considered.

**CONTRAINDICATIONS**  
Rosuvastatin is contraindicated:  
• in patients with hypersensitivity to rosuvastatin or to any of its excipients.  
• in patients with active liver disease (including unexplained, persistent elevations of serum transaminases) and any serum transaminase elevation exceeding 3 times 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 ciclosporin.  
• during pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures.

The 40mg dose is contraindicated in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:  
• moderate renal impairment (creatinine clearance <60 ml/min)  
• 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.

**SPECIAL WARNINGS AND PRECAUTIONS FOR USE**  
**Renal Effects**  
Proteinuria, detected by dipstick testing and mostly labile in origin, has been observed in patients treated with higher doses of Rosuvastatin, in particular 40mg, if it was transient or intermittent in most cases. Proteinuria has not been shown to be predictive of acute or progressive renal disease. The reporting rate for serious renal events in post-marketing use is higher at the 40mg dose. An assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40mg.

**Skeletal Muscle Effects**  
Effects on skeletal muscle, e.g. myalgia, myopathy and, rarely, rhabdomyolysis have been reported in Rosuvastatin-treated patients at all doses and in particular with doses > 20mg. 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 and caution should be exercised with their combined use. As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis associated with Rosuvastatin is post-marketing use is higher at the 40mg 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 (>5xULN) a confirmatory test should be carried out within 5 - 7 days. If the repeat test confirms a baseline (>5xULN) treatment should not be started.

**Before Treatment**  
Rosuvastatin, 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 >70 years  
• situations where an increase in plasma levels may occur  
• 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.

**What to Treat**

Patients should be asked to report intractable muscle pain, weakness or cramps immediately, particularly if associated with nausea or fever. CK levels should be measured in these patients. Therapy should be discontinued if CK levels are markedly elevated (>5000 U/L) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are <5000 U/L). If symptoms resolve and CK levels return to normal, then consideration should be given to re-introducing Rosuvastatin as 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 rhabdomyolysis (RHM) occurring spontaneously, without any other treatment with statins, including rosuvastatin. RHM 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 doses with Rosuvastatin and concomitant therapy. However, an increase in the incidence of myalgia and myopathy has been seen in patients receiving other HMG-CoA reductase inhibitors together with fibrin acid derivatives including gemfibrozil, clopidogrel, niacin acid, azoic antifungals, protease inhibitors and macrolide antibiotics. Gemfibrozil increases the risk of myopathy when given concomitantly with other HMG-CoA reductase inhibitors. Therefore, the combination of Rosuvastatin and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of Rosuvastatin with fibrates or niacin should be carefully weighed against the potential risks of such combinations. The 40mg dose is contraindicated with concomitant use of a fibrate.

Rosuvastatin must not be co-administered with systemic formulations of folic acid or within 7 days of stopping folic acid treatment. In patients where the use of systemic folic acid is considered essential, statin treatment should be discontinued throughout the duration of folic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving folic acid and statins in combination. Patients 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 folic acid. In exceptional circumstances, where prolonged systemic folic acid is needed, e.g. for the treatment of severe infections, the need for co-administration of rosuvastatin and folic acid should only be considered on a case by case basis and under close medical supervision.

Rosuvastatin 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 seizure).

**Liver Effects**

As with other HMG-CoA reductase inhibitors, rosuvastatin 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 should be discontinued or the dose reduced if the level of serum transaminase is greater than 3 times the upper limit of normal. The potential for increased hepatic transaminase (consisting mainly of increased hepatic transaminase) in post-marketing use is higher at the 40mg dose.

In patients with secondary hypercholesterolemia caused by hypothyroidism or nephrotic syndrome, the underlying disease should be treated prior to initiating therapy with rosuvastatin.

**Risk**

Pharmacokinetic studies show an increase in exposure in Asian subjects compared with Caucasians.

**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 inhibitor 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.

**Lactose Intolerance**

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

**Intestinal Lung Disease**

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long-term therapy. 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**

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  $\geq 6.5$  mmol/L, BMI  $> 30$  kg/m<sup>2</sup>, or 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 2.1% in rosuvastatin and 2.3% in placebo, mostly in patients with fasting glucose  $\geq 6.9$  mmol/L.

**Paediatric Population**

The evaluation of linear growth (height), weight, BMI (body mass index), and secondary characteristics of sexual maturation by Tanner staging in paediatric patients to 17 years of age taking rosuvastatin is limited to two-year period. After two years of treatment, no effect on growth, weight, BMI or sexual maturation was detected.

In a clinical trial of children and adolescents receiving rosuvastatin for 52 weeks, CK elevations  $> 10 \times$  ULN and muscle symptoms following exercise or trauma were reported in 4 patients. The frequency was comparable to observations in clinical trials in adults.

**INTERACTION WITH OTHER MEDICAL PRODUCTS AND OTHER FORMS OF INTERACTION:**

**Effect of co-administered medicinal products on rosuvastatin exposure:** 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.

**Cyclosporin:** During concomitant treatment with Rosuvastatin and cyclosporin, rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers. Rosuvastatin is contraindicated in patients receiving concomitant cyclosporin. Concomitant administration did not affect plasma concentrations of cyclosporin.

**Protease inhibitors:** Although the exact mechanism of interaction is unknown, concomitant protease inhibitor use may strongly increase rosuvastatin exposure. For instance, in a pharmacokinetic study, co-administration of 10mg rosuvastatin and a combination product of two protease inhibitors (DORV) (darunavir 100mg (ritonavir) in healthy volunteers was associated with an approximately three-fold and seven-fold increase in rosuvastatin AUC and C<sub>max</sub>, respectively. The concomitant use of rosuvastatin and some protease inhibitors combinations may be considered after careful consideration of rosuvastatin dose adjustments based on the expected increase in rosuvastatin exposure.

**Gemfibrozil and other lipid-lowering products:** Concomitant use of rosuvastatin and gemfibrozil resulted in a 2-fold increase in rosuvastatin C<sub>max</sub> and AUC.

Based on data from specific interaction studies, no pharmacokinetic relevant interaction with fenofibrate is expected. However a pharmacokinetic interaction may occur. Gemfibrozil, fenofibrate, other fibrates and lipid-lowering doses (or equal to 1.5g/day) of niacin (nicotinic acid) increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they may combine myopathy when given alone. The 40mg dose is contraindicated with concomitant use of a fibrate. These patients should also start with the 5mg dose.

**Estimote:** Concomitant use of 10mg rosuvastatin and 10mg estimote resulted in a 1.2-fold increase in AUC of rosuvastatin in hypercholesterolemic subjects. A pharmacodynamic interaction, in terms of adverse effects, between rosuvastatin and estimote cannot be ruled out.

**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 and a 30% decrease in C<sub>max</sub> 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 anti-fibrates (an inhibitor of CYP2C9 and CYP3A4) or ketonolone (an inhibitor of CYP2A6 and CYP3A4). **Interactions requiring rosuvastatin dose adjustments (see also Table 1):** When 1 is necessary to co-administer rosuvastatin with other medicinal products, the concomitant use of rosuvastatin, dose of rosuvastatin should be adjusted. Start with 5mg 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 to that the expected rosuvastatin exposure would not exceed that of a 40mg daily dose (3.1-fold increase) without interacting medicinal products, for example a 20mg dose of rosuvastatin with gemfibrozil (1.8-fold increase), and a 10mg dose of rosuvastatin with concomitant fenofibrate/niacin (3.1-fold increase).

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

| Interacting drug dose regimen   | Rosuvastatin dose regimen | Change in rosuvastatin AUC* |
|---|---------------------------|-----------------------------|
| Cyclosporin 100mg BID to 200mg BID, 8 months                                    | 10mg QD, 7 days           | 7.1-fold ↑                  |
| Atazanavir 300mg/ritonavir 100mg QD, 8 days                                     | 10mg single dose          | 3.8-fold ↑                  |
| Velipristin 100mg QD  | 10mg, single dose         | 3.1-fold ↑                  |
| Colchicine 2mg/day/niacin 1000mg/ritonavir 100mg QD/ezetimibe 40mg BID, 14 days | 5mg, single dose          | 2.6-fold ↑                  |
| Grazoprevir 200mg/sofosbuvir 400mg QD, 11 days                                  | 10mg, single dose         | 2.3-fold ↑                  |
| Cyclosporin 100mg/erythromycin 100mg QD, 7 days                                 | 5mg QD, 7 days            | 2.2-fold ↑                  |
| Lopinavir 400mg/ritonavir 100mg BID, 17 days                                    | 20mg QD, 7 days           | 2.1-fold ↑                  |
| Clopidogrel 300mg loading, followed by 75mg at 24 hours                         | 20mg, single dose         | 2-fold ↑                    |
| Carbamazepine 100mg BID, 7 days   | 80mg, single dose         | 1.9-fold ↑                  |
| Phenazopyridine 100mg QD, 5 days  | 10mg, single dose         | 1.6-fold ↑                  |
| Darunavir 600mg/ritonavir 100mg BID, 7 days                                     | 10mg QD, 7 days           | 1.6-fold ↑                  |
| Tipranavir 500mg/ritonavir 200mg BID, 11 days                                   | 10mg, single dose         | 1.6-fold ↑                  |
| Fluconazole 400mg BID   | 10mg, single dose         | 1.4-fold ↑                  |
| Itraconazole 200mg QD, 14 days  | 10mg, single dose         | **1.4-fold ↑                |
| Fluconazole 100mg/niacin 1000mg BID, 8 days                                     | 10mg, single dose         | **1.2-fold ↑                |
| Atazanavir 300mg, 7 days  | 40mg, 7 days              | ---                         |
| Sildenafil 100mg QD, 5 days   | 10mg, single dose         | ---                         |
| Fenofibrate 100mg TID, 7 days   | 10mg, single dose         | ---                         |
| Estimote 100mg QD, 7 days   | 20mg, single dose         | ---                         |
| Ketoneciclovir 200mg BID, 7 days  | 80mg, single dose         | ---                         |
| Fluconazole 200mg QD, 11 days   | 80mg, single dose         | ---                         |
| Erythromycin 100mg QD, 7 days   | 80mg, single dose         | 20% ↓                       |
| Baclofen 50mg TID, 14 days  | 20mg, single dose         | 40% ↓                       |

\*Data given as a fold change represent a simple ratio between co-administration and rosuvastatin alone. Data given as a % change represent a difference relative to rosuvastatin alone.   
↑ increase is indicated as '↑', no change as '---', decrease as '↓'.   
\*\*Several interaction studies have been performed at different Rosuvastatin dosages, the table shows the most significant effect.   
QD = once daily, BID = twice daily, TID = three times daily, QD = four times daily

**Effect of rosuvastatin on co-administered medicinal products**

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

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

**Other medicinal products:**

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

**Folic Acid:** Interaction studies with rosuvastatin and folic acid have not been conducted. The risk of myopathy, including rhabdomyolysis may be increased by the concomitant administration of systemic folic

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) associated with this combination. If treatment with systemic folic acid is necessary, Rosuvastatin treatment should be discontinued throughout the duration of the folic acid treatment.

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

**FERTILITY, PREGNANCY AND LACTATION:**

Rosuvastatin 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. 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.

**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.

**UNDESIRABLE EFFECTS:**

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.

**Unlabeled list of adverse reactions**

Based on data from clinical studies and extensive post-marketing experience, the following table presents the adverse reaction profile for rosuvastatin. Adverse reactions listed below are classified according to frequency and system organ class (SOC). The frequencies of adverse reactions are ranked according to the following convention: Common ( $\geq 1/100$  to  $< 1/10$ ), Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), Rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), Very rare ( $< 1/10,000$ ), Not known (cannot be estimated from the available data).

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

| System organ class  | Common | Uncommon | Rare | Very rare                                       | Not known  |
|---|--------|----------|------|---|--|
| Blood and lymphatic system disorders  |        |          |      | Thrombocytopenia                                |  |
| Immune system disorders   |        |          |      | Hypersensitivity reactions including angioedema |  |
| Endocrine disorders   |        |          |      | Diabetes mellitus                               |  |
| Psychiatric disorders   |        |          |      |   | Depression   |
| Neurological system disorders   |        |          |      | Headache, Dizziness                             | Postural instability, Sleep disturbances (including insomnia and nightmares) |
| Respiratory, thoracic and respiratory system disorders  |        |          |      |   | Cough, Dyspnoea  |
| Gastro-intestinal disorders   |        |          |      | Constipation, Nausea, Abdominal pain            | Diarrhoea  |
| Hepatology disorders  |        |          |      | Increased hepatic transaminases                 | Jaundice, Hepatitis  |
| Skin and subcutaneous tissue disorders  |        |          |      | Pruritus, Rash, Urticaria                       | Dermatitis, Johnson syndrome   |
| Musculo-skeletal and connective tissue disorders  |        |          |      | Myalgia   | Arthralgia, Myopathy (including myositis), Rhabdomyolysis                    |
| Renal and urinary disorders   |        |          |      |   | Haematuria   |
| Reproductive system and breast disorders  |        |          |      |   | Gynaecostoma   |
| General disorders and administration site conditions  |        |          |      |   | Oedema   |
| Frequency may depend on the frequency or duration of use, factors relating to local glucose $\geq 6.5$ mmol/L, BMI $> 30$ kg/m <sup>2</sup> , raised triglycerides, history of hypertension |        |          |      |   |  |

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 labular in origin, has been observed in patients treated with Rosuvastatin. Slight increase in urine protein from none or trace to + or more were seen in <1% of patients at some time during treatment with 10 and 20mg, and in approximately 3% of patients treated with 40mg. A minor increase in urine protein to + was observed with the 20mg dose. In most cases, proteinuria decreased or disappeared 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 patients with doses  $\geq 20$ 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 (>500 U/L), treatment should be discontinued.

**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.

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

**Paediatric population:** Creative kinase elevation  $> 10 \times$  ULN and mild symptoms following exercise or increased physical activity were observed more frequently in a 52-week clinical trial of children and adolescents compared to adults. In other respects, the safety profile of rosuvastatin was similar in children and adolescents compared to adults.

**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 initiated as required. Liver function and CK levels should be monitored. Haemodialysis is unlikely to be of benefit.

**CLINICAL PHARMACOLOGY:**

**Pharmacotherapeutic group:** HMG-CoA reductase inhibitors

**ATC code:** C10AA07

**PHARMACODYNAMICS:**

**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 VLDL, and inhibits the hepatic synthesis of VLDL, thereby reducing the total number of LDL and VLDL particles.

**Pharmacodynamic effects**

Rosuvastatin reduces elevated LDL cholesterol, total cholesterol and triglycerides and increases HDL cholesterol. It also lowers ApoB, non-HDL, VLDL-C, LDL-C/TG and increases ApoA1/ApoB. Rosuvastatin also lowers the LDL-C/HDL-C, total CHOL-C and non-HDL-C/HDL-C and the ApoB/ApoA1-ratios.

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

| Dose    | N  | LDL-C | Total | HDL-C | TG  | nonHDL-C | ApoB | ApoA1 |
|---------|----|-------|-------|-------|-----|----------|------|-------|
| Placebo | 13 | -7    | -6    | 3     | -3  | -7       | -7   | 3     |
| 5       | 17 | -45   | -33   | 13    | -39 | -44      | -38  | 4     |
| 10      | 17 | -52   | -39   | 15    | -42 | -47      | -41  | 5     |
| 20      | 17 | -65   | -43   | 8     | -23 | -51      | -46  | 5     |
| 40      | 18 | -63   | -48   | 10    | -28 | -50      | -44  | 5     |

A therapeutic effect is obtained within 1 week following treatment initiation and 90% of maximum response is achieved at 2 weeks. The maximum response is usually achieved by 4 weeks and is maintained after 8 weeks.

**Clinical efficacy and safety**

Rosuvastatin is effective in adults with hypercholesterolemia, with and without hypertriglyceridemia, regardless of race, sex or age and in special populations such as diabetics or patients with familial hypercholesterolemia.

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

In a large study, 432 patients with heterozygous familial hypercholesterolemia were given Rosuvastatin from 20mg to 80mg in a force-titration design. All doses showed a beneficial effect on lipid parameters and had treatment to target. Following titration to a daily dose of 40mg (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 (including 8 paediatric patients) with homozygous familial hypercholesterolemia were evaluated for their response to Rosuvastatin 20 - 40mg. 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.

In a multi-centre, double-blind, placebo-controlled clinical study (MIEOTER), 984 patients between 45 and 70 years of age and at low risk for coronary heart disease (defined as Framingham risk  $< 10\%$  over 10 years) with a mean LDL-C of 4.0 mmol/L ( $154$  mg/dL), but with subclinical atherosclerosis (detected by Carotid Intima Media Thickness) were randomised to 40mg rosuvastatin or 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: 0.006, 0.003,  $p < 0.001$ ). The change from baseline was  $< 0.0014$  mm/year (0.12% per year) (non-significantly) for rosuvastatin compared to a progression of  $< 0.0131$  mm/year (1.02% per year) ( $p < 0.001$ ) for placebo. No direct correlation between CIMT decrease and reduction of the risk of cardiovascular events has yet been demonstrated.

The population study of MIEOTER is low risk for coronary heart disease and does not represent the target population of the Rosuvastatin 40mg. The 40mg dose should only be prescribed in patients with severe hypercholesterolemia at high cardiovascular risk.

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 (80 years) and women (60 years).

Study participants were randomly assigned to placebo (n=8907) or rosuvastatin 20mg once daily (n=8907) 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  $> 20\%$  (1688 subjects) there was a significant reduction in the combined end-point of cardiovascular death, stroke and myocardial infarction (p=0.02) on rosuvastatin treatment versus placebo. The absolute risk reduction in the event rate was 0.0014 mm/year (0.12% per year) (non-significantly) for rosuvastatin compared to a progression of 0.0014 mm/year (0.12% per year) (non-significantly) for placebo. There was a significant reduction in the combined end-point of cardiovascular death, stroke and myocardial infarction (p=0.003) on rosuvastatin