Package Insert

CRESCORD 5, 10, 20
Rosuvastatin film coated Tablets 5mg, 10mg and 20 mg

NAME AND STRENGTH OF ACTIVE INGREDIENT

CRESCORD 5: Rosuvastatin Calcium eq. to Rosuvastatin 5 mg
CRESCORD 10: Rosuvastatin Calcium eq. to Rosuvastatin 10 mg
CRESCORD 20: Rosuvastatin Calcium eq. to Rosuvastatin 20 mg

PRODUCT DESCRIPTION

CRESCORD 5: Yellow, round, biconvex, film-coated tablet, debossed "5" on one side and "R" on other side. Thickness: 4.00 mm ± 0.30 mm

CRESCORD 10: Pink, round, biconvex, film-coated tablet, debossed "10" on one side and "R" on other side. Thickness: 4.00 mm ± 0.30 mm

CRESCORD 20: Pink, round, biconvex, film-coated tablet, debossed "20" on one side and "R" on other side. Thickness: 4.85 mm ± 0.3 mm

THERAPEUTIC INDICATIONS

Crescord (rosuvastatin calcium) is indicated as an adjunct to diet, at least equivalent to the Adult Treatment Panel III (ATP III TLC diet), for the reduction of elevated total cholesterol, LDL-cholesterol, ApoB, the total cholesterol: HDL-cholesterol ratio and triglycerides and for increasing HDL-C, in hyperlipidemic and dyslipidemic conditions, when response to diet and exercise alone has been inadequate including:

Prevention of Cardiovascular Events. In adult patients with an increased risk of atherosclerotic cardiovascular disease based on the presence of cardiovascular disease risk markers such as an elevated hsCRP level, age, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease, Crescord is indicated to reduce total mortality and the risk of major cardiovascular events (cardiovascular death, stroke, MI, unstable angina, or arterial revascularization)

Crescord is indicated as an adjunct to diet for the treatment of patients with primary dysbetalipoproteinemia (Type III Hyperlipoproteinemia).

Primary hypercholesterolaemia (Type IIa including heterozygous familial hypercholesterolaemia and severe non-familial hypercholesterolaemia)

Combined (mixed) dyslipidemia (Type IIb)

Homozygous familial hypercholesterolaemia where Crescord is used either alone or as an adjunct to diet and other lipid lowering treatment such as apheresis.

Crescord is indicated as adjunctive therapy to diet to slow the progression of atherosclerosis in adult patients as part of a treatment strategy to lower Total-C and LDL-C to target levels.

Pediatric Patients 10 to 17 years of age with Heterozygous Familial Hypercholesterolemia (HeFH): Adjunct to diet to reduce Total-C, LDL-C and ApoB levels in adolescent boys and girls, who are at least one year post-menarche, 10-17 years of age with heterozygous familial hypercholesteroleamia if after an adequate trial of diet therapy the following findings are present: LDL-C > 190 mg/dL or > 160 mg/dL and there is a positive family history of premature cardiovascular disease (CVD) or two or more other CVD risk factors.

POSOLOGY AND METHOD OF ADMINISTRATION

Route of Administration
Oral

Patients should be placed on a standard cholesterol-lowering diet (at least equivalent to the Adult Treatment Panel III (ATP III TLC diet)) before receiving Crescord, and should continue on this diet during treatment with Crescord. If appropriate, a program of weight control and physical exercise should be implemented.

Prior to initiating therapy with Crescord, secondary causes for elevations in plasma lipid levels should be excluded. A lipid profile should also be performed. After initiation or upon titration of Crescord, lipid levels should be analyzed within 2-4 weeks and the dosage adjusted accordingly.

The usual recommended starting dose of Crescord is 10 mg once daily. However, initiation of therapy with 5 mg once daily should be considered for special patient populations or patients requiring less aggressive LDL-C reductions. The choice of starting dose should take into account the individual patients' cholesterol level and future cardiovascular risk as well as the potential risk for adverse reactions. Crescord may be taken in the morning or evening, with or without food. The majority of patients are controlled at the 10 mg dose. However, if necessary, dose adjustments to the next dose level can be made after 4-week intervals. The maximum response is usually achieved within 2-4 weeks and is maintained during chronic therapy. Increasing the dose to 40 mg should be reserved for 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 should only be initiated under specialist supervision (see *Special Warnings and Precautions for Use*). The physician who elects to use Crescord at a dose higher than 20 mg should periodically re-evaluate the long term risk/benefit of Crescord for the individual patient. Crescord should be prescribed with caution in patients with pre-disposing factors for myopathy / rhabdomyolysis (see *Special Warnings and Precautions for Use*).

The dosage of Crescord should be individualised according to baseline LDL-C, total-C/HDL-C ratio and/or TG levels, the recommended target lipid values (see *Recommendations for the Management and Treatment of Dyslipidemia [Canada]* summarised below in Table 1) and/or the

Third Report of the U.S. National Cholesterol Education Program [NCEP Adult Treatment Panel III]) and the patient response.

The majority (80%) of patients treated with rosuvastatin 10 mg achieved their NCEP ATP III treatment target for LDL-C levels; fewer subjects (68%) achieved target on the 5 mg dose. The difference between rosuvastatin 5 mg and 10 mg was greatest for high risk subjects (40% versus 61%, respectively), i.e. for subjects who have a lower LDL-C target.

Lipid levels should be monitored periodically and, if necessary, the dose of Crescord adjusted based on target lipid levels recommended by guidelines.

Table 1: Canadian Recommendations for Target Lipid Values Based on Level of Risk

Level of Risk (definition)	**Target values LDL-C (mmol/L)**	**Total-C/ HDL-C ratio**	**TG (mmol/L)**
Very high* (10-year risk of CAD>30%, or history of cardiovascular disease or diabetes)	<2.5	<4.0	<2.0
High* (10-year risk CAD 20% - 30%)	<3.0	<5.0	<2.0
Moderate** (10-year risk of CAD 10% - 20%)	<4.0	<6.0	<2.0
Low*** (10-year risk of CAD <10%)	<5.0	<7.0	<3.0

*Start medication and lifestyle changes concomitantly if values are above target values
**Start medication if target values are not achieved after 3 months of lifestyle modification
***Start medication if target values are not achieved after 6 months of lifestyle modification

The following reductions in total cholesterol, LDL-C, TG, Total-C/HDL and increases in HDL-C have been observed in a dose-response study, and may serve as a guide to treatment of patients with mild to moderate hypercholesterolaemia:

Table 2: Dose-Response in Patients with Mild to Moderate Hypercholesterolaemia (Mean Percent change from Baseline)

Dose (mg/day)	**N**	**Total-C**	**LDL-C**	**TG**	**HDL-C**	**Total-C/HDL-C**	**Apo B**
Placebo	13	-5	-7	-3	3	-8	-3
5	17	-33	-45	-35	13	-41	-38
10	17	-36	-52	-10	14	-43	-42
20	17	-40	-55	-23	8	-44	-46
40	18	-46	-63	-28	10	-51	-54

Dosage in patients with renal insufficiency
The usual dose range applies in patients with mild to moderate renal impairment.

For patients with severe renal impairment (CLcr <30 mL/min/1.73 m^2) not on hemodialysis, dosing of Crescord should be started at 5 mg once daily and not exceed 10 mg once daily (see *Pharmacokinetic Properties*).

Dosage in patients with hepatic insufficiency
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. In these patients an assessment of renal function should be considered. There is no experience in subjects with Child-Pugh scores above 9. Crescord is contraindicated in patients with active liver disease.

Use in the elderly
Of the 10,275 patients in clinical studies with rosuvastatin, 3,159 (31%) were 65 years and older, and 698 (6.8%) were 75 years and older. The overall frequency of adverse events and types of adverse events were similar in patients above and below 65 years of age. The efficacy of rosuvastatin in the geriatric population (≥65 years of age) was comparable to the efficacy observed in the non-elderly.

Pediatric patients (10 to 17 years of age)
In pediatric patients (10 to 17 years of age) with heterozygous familial hypercholesterolemia the usual dose range of Crescord is 5-20 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in this patient population). Doses should be individualized according to the recommended goal of therapy (see *Clinical Efficacy* and *Therapeutic Indications*). Adjustments should be made at intervals of 4 weeks or more.

Use in children below 10 years
The safety and effectiveness in children have not been established. In children and adolescents with homozygous familial hypercholesterolemia experience is limited to eight patients (aged 8 years and above).

Dosage on Asian patients
Initiation of Crescord therapy with 5 mg once daily should be considered for Asian patients. The potential for increased systemic exposures relative to Caucasians is relevant when considering escalation of dose in cases where hypercholesterolaemia is not adequately controlled at doses of 5, 10 or 20 mg once daily (see *Special warnings and special precautions for use* and *Pharmacokinetic properties*).

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

Dosage in patients with pre-disposing factors to myopathy
The recommended start dose is 5 mg in patients with predisposing factors to myopathy (see *Special Warnings and Special Precautions for Use*).

Concomitant therapy
Rosuvastatin is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when Crescord is administered concomitantly with certain medicinal products that may increase the plasma concentration of rosuvastatin due to interactions with these transporter proteins (e.g. ciclosporin and certain protease inhibitors including combinations of ritonavir with atazanavir, lopinavir, and/or tipranavir; see *Special Warnings and Special Precautions for Use* and *Interaction with Other Medicinal Products and Other Forms of Interaction*). Whenever possible, alternative medications should be considered, and, if necessary, consider temporarily discontinuing Crescord therapy. In situations where co-administration of these medicinal products with Crescord is unavoidable, the benefit and the risk of concurrent treatment and Crescord dosing adjustments should be carefully considered (see *Interaction with Other Medicinal Products and Other Forms of Interaction*). If concomitant use of Crescord with ciclosporin cannot be avoided, the dose of Crescord should not exceed 5 mg once daily (see *Special Warnings and Special Precautions for Use* and *Interaction with Other Medicinal Products and Other Forms of Interactions*).

CONTRAINDICATIONS

Crescord is contraindicated in patients with hypersensitivity to any component of this product.
Crescord is contraindicated in patients with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3x the upper limit of normal (ULN).
Crescord is contraindicated during pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures.
Crescord is contraindicated in patients with myopathy.
Crescord is contraindicated in patients receiving concomitant cyclosporine.

SPECIAL WARNINGS AND SPECIAL 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 Calcium, 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. An assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40 mg.

Renal impairment
Rosuvastatin exposure is not influenced by mild to moderate renal impairment (CLcr ≥30 mL/min/1.73 m^2). Exposure to rosuvastatin is increased to a clinically significant extent in patients with severe renal impairment (CLcr <30 mL/min/1.73 m^2) who are not receiving hemodialysis and dose adjustment is required (see *Posology and Method for Administration*, and *Pharmacokinetic Properties*.

Skeletal muscle effects
Gemfibrozil increases the risk of myopathy when given concomitantly with some HMG-CoA reductase inhibitors. Therefore, the combination of rosuvastation and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of rosuvastation with fibrates or niacin should be carefully weighed against the potential risks of such combinations.

Effects on skeletal muscle e.g. myalgia, myopathy and, rarely, rhabdomyolysis have been reported in Rosuvastatin Calcium-treated patients with all doses and in particular with doses >20 mg. Very rare cases of rhabdomyolysis have been reported with the use of ezetimibe in combination with HMG-CoA reductase inhibitors. A pharmacodynamic interaction cannot be excluded (see *Interaction with Other Medicinal Products and Other Forms of Interaction*) and caution should be exercised with their combined use. As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis associated with Rosuvastatin Calcium 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 (>5 x ULN) a confirmatory test should be carried out within 5 – 7 days. If the repeat test confirms a baseline CK >5 x ULN, treatment should not be started.

Before Treatment
Rosuvastatin Calcium, 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 (see *Posology and Method of Administration, Interaction with Other Medicinal Products and Other Forms of Interaction* and *Pharmacokinetic Properties*).
- 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 (>5 x ULN) or if muscular

symptoms are severe and cause daily discomfort (even if CK levels are ≤5 x ULN). If symptoms resolve and CK levels return to normal, then consideration should be given to re-introducing Rosuvastatin Calcium 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 some statins, including rosuvastatin. IMNM is clinically characterised by:

- persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment;
- muscle biopsy showing necrotizing myopathy without significant inflammation;
- improvement with immunosuppressive agents.

In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia (*Clinical Adverse Experiences*). Rosuvastatin calcium should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported.

In clinical trials there was no evidence of increased skeletal muscle effects in the small number of patients dosed with Rosuvastatin Calcium 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 Calcium and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of Rosuvastatin Calcium with fibrates or niacin should be carefully weighed against the potential risks of such combinations (see *Posology and Method of Administration*, *Interaction with Other Medicinal Products and Other Forms of Interaction* and *Clinical Adverse Experiences*).

Rosuvastatin Calcium 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, Rosuvastatin Calcium 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 Calcium 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 Rosuvastatin Calcium.

Race
Pharmacokinetic studies show an increase in exposure in Asian subjects compared with Caucasians (see *Posology and Method of Administration*, and *Pharmacokinetic Properties*).

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 Calcium in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up titrating Rosuvastatin Calcium doses in patients treated with protease inhibitors. The concomitant use with certain protease inhibitors is not recommended unless the dose of Rosuvastatin Calcium is adjusted. (See *Posology and Method of Administration* and *Interaction with Other Medicinal Products and Other Forms of Interaction*)

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

Interstitial lung disease
Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see C*linical Adverse Experiences*). 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 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

Pediatric patients (10 to 17 years of age)
The evaluation of linear growth (height), weight, BMI (body mass index), and secondary characteristics of sexual maturation by Tanner staging in pediatric patients taking rosuvastatin is limited to a one year period.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Effect of co-administered medicinal products on rosuvastatin

Transporter protein inhibitors: Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter OATP1B1 and efflux transporter BCRP. Concomitant administration of Rosuvastatin Calcium with medicinal products that are inhibitors of these transporter proteins may result in increased rosuvastatin plasma concentrations and an increased risk of myopathy (see *Posology and Method of Administration, Special Warnings and Special Precautions for Use* and *Interaction with Other Medicinal Products and Other Forms of Interaction Table 3*).

Ciclosporin: Ciclosporin increased rosuvastatin exposure and may result in increased risk of myopathy (see Table 3). Therefore, in patients taking ciclosporin, the dose of Rosuvastatin Calcium should not exceed 5 mg once daily (see *Posology and Method of Administration* and *Special Warnings and Special Precautions for Use*).

Protease inhibitors: Although the exact mechanism of interaction is unknown, concomitant protease inhibitor use may strongly increase rosuvastatin exposure (see Table 3). 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 AUC and Cmax respectively. The concomitant use of Rosuvastatin Calcium and some protease inhibitor combinations may be considered after careful consideration of Rosuvastatin Calcium dose adjustments based on the expected increase in rosuvastatin exposure (see *Posology and Method of Administration, Special Warnings and Special Precautions for Use* and *Interaction with Other Medicinal Products and Other Forms of Interaction Table 3*).

Gemfibrozil and other lipid-lowering products: Concomitant use of Rosuvastatin Calcium and gemfibrozil resulted in a 2-fold increase in rosuvastatin Cmax and AUC (see *Special Warnings and Special Precautions for Use*). Based on data from specific interaction studies no pharmacokinetic relevant interaction with fenofibrate is expected, however a pharmacodynamic interaction may occur. Gemfibrozil, fenofibrate, other fibrates and lipid lowering doses (> or equal to 1g/day) of niacin (nicotinic acid) increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone. These patients should also start with the 5 mg dose.

Ezetimibe: Concomitant use of 10 mg Rosuvastatin Calcium and 10 mg ezetimibe resulted in a 1.2 fold increase in AUC of rosuvastatin in hypercholesterolaemic subjects (Table 3). A pharmacodynamic interaction, in terms of adverse effects, between Rosuvastatin Calcium and ezetimibe cannot be ruled out (see *Special Warnings and Special Precautions for Use*).

Antacid: The simultaneous dosing of Rosuvastatin Calcium 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 Calcium. The clinical relevance of this interaction has not been studied.

Fusidic Acid: Interaction studies with rosuvastatin and fusidic acid have not been conducted. As with other statins, muscle related events, including rhabdomyolysis, have been reported in post-marketing experience with rosuvastatin and fusidic acid given concurrently. Patients should be closely monitored and temporary suspension of rosuvastatin treatment may be appropriate.

Erythromycin: Concomitant use of Rosuvastatin Calcium and erythromycin resulted in a 20% decrease in AUC (0-t) and a 30% decrease in Cmax of rosuvastatin. This interaction may be caused by the increase in gut motility caused by erythromycin.

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

Interactions requiring rosuvastatin dose adjustments (see also Table 3):
When it is necessary to co-administer rosuvastatin with other medicinal products known to increase exposure to rosuvastatin, doses of rosuvasatin should be adjusted. It is recommended that prescribers consult the relevant product information when considering administration of such products together with rosuvasatin.

If medicinal product is observed to increase rosuvastatin AUC approximately 2-fold or higher, the starting dose of rosuvasatin should not exceed 5 mg once daily. 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 5 mg dose of rosuvastatin with ciclosporin (7.1-fold increase in exposure), a 10 mg dose of rosuvastatin with ritonavir/atazanavir combination (3.1-fold increase) and a 20 mg dose of rosuvastatin with gemfibrozil (1.9-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 20mg.
Protease Inhibitors: Coadministration of rosuvastatin with certain protease inhibitors or combination of protease inhibitors may increase the rosuvastatin exposure, (AUC) up to 7-fold (*see Table1*). Dose adjustment are needed depending on the level of effect on rosuvastatin exposure (*see Posology and Method of Administration and Special Warnings and Special Precautions For Use*)

Table 3: 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	7.39 -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	5mg, single dose	5.2-fold ↑
Regorafenib 160 mg OD, 14 days	5mg, single dose	3.8 -fold ↑
Atazanavir 300 mg/ritonavir 100 mg OD, 8 days	10 mg, single dose	3.1-fold ↑
Simeprevir 150 mg OD, 7 days	10 mg, single dose	2.8-fold ↑
Velpatasvir 100 mg OD	10 mg single dose	2.69 -fold ↑
Ombitasvir 25 mg/paritaprevir 150 mg/ritonavir 100 mg/dasabuvir 400 mg BID	5 mg single dose	2.59-fold ↑
Teriflunomide	Not available	2.5-fold ↑
Grazoprevir 200 mg/elbasvir 50 mg OD	10 mg single dose	2.26-fold ↑
Glecaprevir 400 mg/pibrentasvir 120 mg OD for 7 days	5mg once daily	2.2-fold ↑
Lopinavir 400 mg/ritonavir 100 mg BID, 17 days	20 mg OD, 7 days	2.1-fold ↑
Capmatinib 400mg BID	10mg, single dose	2.1-fold ↑
Clopidogrel 300 mg loading, followed by 75 mg at 24 hours [3]	20 mg, single dose[3]	2-fold ↑
Fostamatinib 100 mg twice daily	20 mg, single dose	2.0-fold ↑
Febuxostat 120mg OD	10 mg, single dose	1.9-fold ↑
Gemfibrozil 600 mg BID, 7 days	80 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 day	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 Calcium 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

The following medicinal 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.

Other medications: Concurrent use of fibrates may cause severe myositis and myoglobinuria.

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 Calcium 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 Calcium 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 Calcium 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 Calcium 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.

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

USE DURING PREGNANCY AND LACTATION

The safety of Rosuvastatin Calcium during pregnancy and whilst breast-feeding has not been established. Women of child-bearing potential should use appropriate contraceptive measures (See *Contraindications*).

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Pharmacology testing revealed no evidence of a sedative effect of Rosuvastatin Calcium. From the safety profile, Rosuvastatin Calcium is not expected to adversely affect the ability to drive or use machines.

CLINICAL ADVERSE EXPERIENCES

There have been rare post-marketing reports of cognitive impairment (e.g. memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These issues have been reported for all statins. The reports are generally non-serious and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median 3 weeks).

Increases in HbA1c and fasting blood glucose have been reported with statins. The risk of hyperglycemia, however, is outweighed by the reduction in vascular risk with statins.

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

Tabulated 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 (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1000); Very rare (<1/10,000); Not known (cannot be estimated from the available data).

Table 4: 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			Hypersensitivity		

disorders			reactions including angioedema		
Endocrine disorders	Diabetes mellitus[1]				
Psychiatric disorders					Depression
Nervous system disorders	Headache Dizziness			Polyneuropathy Memory loss	Sleep disturbances (including insomnia and nightmares) Peripheral neuropathy Myasthenia gravis
Eye diorders					Ocular myasthenia
Respiratory, thoracic and mediastinal disorders					Cough Dyspnoea
Gastro-intestinal disorders	Constipation Nausea Abdominal pain		Pancreatitis		Diarrhoea
Hepatobiliary disorders			Increased hepatic transaminases	Jaundice Hepatitis	
Skin and subcutaneous tissue disorders		Pruritis Rash Urticaria			Stevens-Johnson syndrome, Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculo-skeletal and connective tissue disorders	Myalgia		Myopathy (including myositis) Rhabdomyolysis	Arthralgia	Immune-mediated necrotising myopathy
Renal and urinary				Haematuria	

disorders					
Reproductive system and breast disorders				Gynaecomastia	
General disorders and administration site conditions	Asthenia				Oedema

[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 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 Calcium. 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 Calcium 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 Calcium-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 (>5 x ULN), treatment should be discontinued (see *Special Warnings and Special Precautions for Use*).

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 *Special Warnings and Special Precautions for Use*).

Tendon disorders, sometimes complicated by rupture.

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.

Pediatric patients 10 to 17 years of age: In a 12-week controlled study in boys and postmenarchal girls, the safety and tolerability profile of ROSUVASTATIN CALCIUM 5 to 20 mg daily was generally similar to that of placebo (see *Clinical Efficacy and Pharmacokinetic - Special Populations*)

However, elevations in serum creatine phosphokinase (CK) >10 x ULN were observed more frequently in rosuvastatin compared with placebo-treated children. Four of 130 (3%) children treated with rosuvastatin (2 treated with 10 mg and 2 treated with 20 mg) had increased CK >10 x ULN, compared to 0 of 46 children on placebo.

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. Haemodialysis is unlikely to be of benefit.

PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: HMG-CoA reductase inhibitors
ATC code: C10A A07

Mechanism of action:
Rosuvastatin is a selective, potent and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. Triglycerides (TG) and cholesterol in the liver are incorporated, with apolipoprotein B (ApoB), into very low density lipoprotein (VLDL) and released into the plasma for delivery to peripheral tissues. VLDL particles are TG-rich. Cholesterol-rich low density lipoprotein (LDL) is formed from VLDL and is cleared primarily through the high affinity LDL receptor in the liver.

Rosuvastatin produces its lipid-modifying effects in two ways; it 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.

High density lipoprotein (HDL), which contains ApoA-I is involved, amongst other things, in transport of cholesterol from tissues back to the liver (reverse cholesterol transport).

The involvement of LDL-C in atherogenesis has been well documented. Epidemiological studies have established that high LDL-C, TG, low HDL-C and ApoA-I have been linked to a higher risk of cardiovascular disease. Intervention studies have shown the benefits on mortality and CV event rates of lowering LDL-C and TG or raising HDL-C. More recent data has linked the beneficial effects of HMG-CoA reductase inhibitors to lowering of non-HDL (i.e. all circulating cholesterol not in HDL) and ApoB or reducing the ApoB/ApoA-I ratio.

Clinical efficacy:

Rosuvastatin Calcium 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 Tables 5 and 6).

Rosuvastatin Calcium also lowers the LDL -C/HDL-C, total C/HDL-C, nonHDL-C/HDL-C and ApoB / ApoA-I ratio's.

A therapeutic response to Rosuvastatin Calcium is evident within 1 week of commencing therapy and 90% of maximum response is usually achieved in 2 weeks. The maximum response is usually achieved by 4 weeks and is maintained after that.

Table 5: 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**	**Non HDL-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

Table 6: Dose Response in Patients with Hypertriglyceridaemia (Type IIb or Type IV) (Median % change from baseline)

Dose	**N**	**LDL-C**	**Total-C**	**HDL-C**	**TG**	**Non HDL-C**	**VLDL-C**	**VLDL-TG**
Placebo	26	5	1	-3	1	2	2	6
5	25	-28	-24	3	-21	-29	-25	-24
10	23	-45	-40	8	-37	-49	-48	-39
20	27	-31	-34	22	-37	-43	-49	-40
40	25	-43	-40	17	-43	-51	-56	-48

The data in Tables 5 and 6 are confirmed by the broader clinical programme of over 5,300 patients given Rosuvastatin Calcium.

In a study of patients with heterozygous familial hypercholesterolaemia, 435 subjects were given Rosuvastatin Calcium from 20 mg to 80 mg in a force-titration design. All doses of Rosuvastatin Calcium showed a beneficial effect on lipid parameters and treatment to target goals. Following titration to 40 mg (12 weeks of treatment) LDL-C was reduced by 53%.

In a force-titration open label study, 42 patients with homozygous familial hypercholesterolaemia were evaluated for their response to Rosuvastatin Calcium 20 - 40 mg titrated at a 6 week interval. In the overall population, the mean LDL-C reduction was 22%. In the 27 patients with at least a 15% reduction by week 12 (considered to be the responder population), the mean LDL-C reduction was 26% at the 20 mg dose and 30% at the 40 mg dose. Of the 13 patients with an LDL-C of less than 15%, 3 had no response or an increase in LDL-C.

In a randomized, multi-center, double-blind crossover study, 32 patients (27 with ε2/ε2 and 4 with apo E mutation [Arg145Cys] with primary dysbetalipoproteinemia (Type III Hyperlipoproteinemia) entered a 6-week dietary lead-in period on the NCEP Therapeutic Lifestyle Change (TLC) diet. Following dietary lead-in, patients were randomized to a sequence of treatments in conjunction with the TLC diet for 6 weeks each: rosuvastatin 10 mg followed by rosuvastatin 20 mg or rosuvastatin 20 mg followed by rosuvastatin 10 mg. Rosuvastatin Calcium reduced nonHDL-C (primary endpoint) and circulating remnant lipoprotein levels. Results are shown in the table below.

Table 7: Lipid-modifying Effects of Rosuvastatin 10 mg and 20 mg in Primary Dysbetalipoproteinemia (Type III hyperlipoproteinemia) after Six weeks by Median Percent Change (95% CI) from Baseline (N=32)

	Median at Baseline (mg/dL)	**Median percent change from baseline (95 % CI) Rosuvastatin Calcium 10 mg**	**Median percent change from baseline (95% CI) Rosuvastatin Calcium 20 mg**
Total-C	342.5	-43.3 (-46.9, -37.5)	-47.6 (-51.6, -42.8)
Triglycerides	503.5	-40.1 (-44.9, -33.6)	-43.0 (-52.5, -33.1)
Non-HDL-C	294.5	-48.2 (-56.7, -45.6)	-56.4 (-61.4, -48.5)
VLDL-C + IDL-C	209.5	-46.8 (-53.7, -39.4)	-56.2 (-67.7, -43.7)
LDL-C	112.5	-54.4 (-59.1, -47.3)	-57.3 (-59.4, -52.1)
HDL-C	35.5	10.2 (1.9, 12.3)	11.2 (8.3, 20.5)
RLP-C	82.0	-56.4 (-67.1, -49.0)	-64.9 (-74.0, -56.6)
Apo-E	16.0	-42.9 (-46.3, -33.3)	-42.5 (-47.1, -35.6)

In the Measuring Effects on Intima Media Thickness: an Evaluation Of Rosuvastatin 40 mg (METEOR) study, the effect of therapy with Rosuvastatin Calcium on carotid atherosclerosis was assessed by B-mode ultrasonography in patients with elevated LDL-C, at low risk (Framingham risk <10% over ten years) for symptomatic coronary artery disease and with subclinical atherosclerosis as evidenced by carotid intimal-medial thickness (cIMT). In this double-blind, placebo-controlled clinical study 984 patients were randomized (of whom 876 were analyzed) in a 5:2 ratio to Rosuvastatin Calcium 40 mg or placebo once daily. Ultrasonograms of the carotid walls were used to determine the annualized rate of change per patient from baseline to two years in mean maximum cIMT of 12 measured segments. The estimated difference in the rate of change in the maximum cIMT analyzed over all 12 carotid artery sites between Rosuvastatin Calcium-treated patients and placebo-treated patients was -0.0145 mm/year (95% Confidence Interval CI –0.0196, –0.0093; p<0.0001).

The annualized rate of change from baseline for the placebo group was +0.0131 mm/year (p<0.0001). The annualized rate of change from baseline for the Rosuvastatin Calcium group was -0.0014 mm/year (p=0.32).

At an individual patient level in the Rosuvastatin Calcium group, 52.1% of patients demonstrated an absence of disease progression (defined as a negative annualized rate of change), compared to 37.7% of patients in the placebo group.

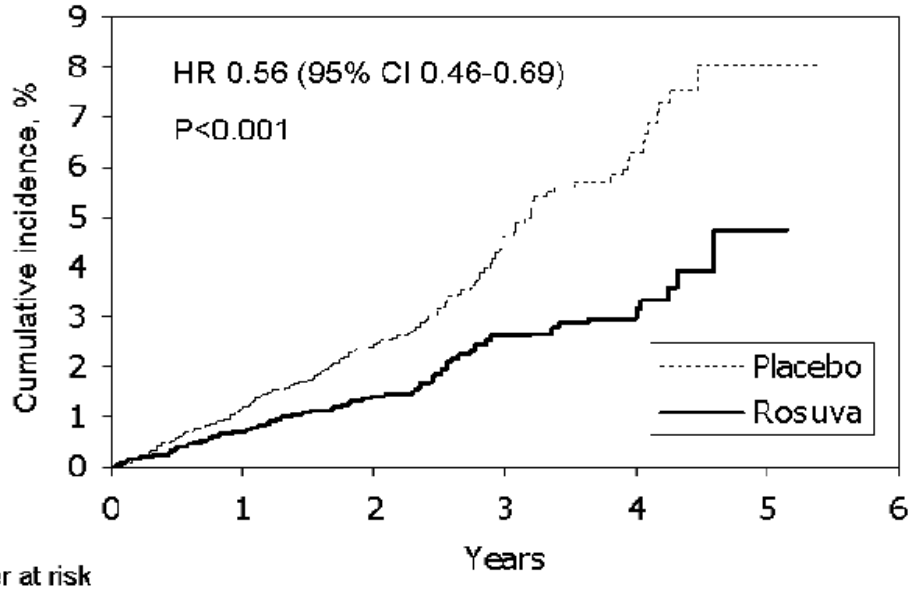
Rosuvastatin Calcium is effective in a wide variety of patient populations with hypercholesterolaemia, with and without hypertriglyceridaemia, regardless of race, sex or age and in special populations such as diabetics or patients with familial hypercholesterolaemia.

In the **J**ustification for the **U**se of Statins in **P**rimary Prevention: An **I**ntervention **T**rial **E**valuating **R**osuvastatin (JUPITER) study, the effect of rosuvastatin calcium on the occurrence of major atherosclerotic cardiovascular (CV) disease events was assessed in 17,802 men (≥50 years) and women (≥60 years) who had no established cardiovascular disease, LDL-C levels <130 mg/dL (3.3 mmol/l) and hs-CRP levels ≥2 mg/L. The study population had an estimated baseline coronary heart disease risk of 11.3% over 10 years based on the Framingham risk criteria and included a high percentage of patients with additional risk factors such as hypertension (58%), low HDL-C levels (23%), cigarette smoking (16%) or a family history of premature CHD (12%). 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.

The primary endpoint was a composite endpoint consisting of the time-to-first occurrence of any of the following CV events: CV death, non-fatal myocardial infarction, non-fatal stroke, unstable angina or an arterial revascularization procedure.

Rosuvastatin significantly reduced the risk of CV events (252 events in the placebo group vs. 142 events in the rosuvastatin group) with a statistically significant ($p<0.001$) relative risk reduction of 44% (see Figure 1). The benefit was apparent within the first 6 months of treatment. The risk reduction was consistent across multiple predefined population subsets based on assessments of age, sex, race, smoking status, family history of premature CHD, body mass index, LDL-C, HDL-C or hsCRP levels at the time of entry into the study. There was a statistically significant 48% reduction in the combined endpoint of CV death, stroke and myocardial infarction (HR: 0.52, 95% CI: 0.40-0.68, $p<0.001$), a 54% reduction in fatal or nonfatal myocardial infarction (HR: 0.46, 95% CI: 0.30-0.70) and a 48% reduction in fatal or nonfatal stroke. Total mortality was reduced 20% in the rosuvastatin group (HR: 0.80, 95% CI: 0.67- 0.97, $p=0.02$).

Figure 1: Time to occurrence of major cardiovascular events in JUPITER



The safety profile for subjects taking rosuvastatin 20 mg was generally similar to that of subjects taking placebo. There were 1.6% of rosuvastatin and 1.8% of placebo subjects who withdrew from the trial due to an adverse event, irrespective of treatment causality. The most common adverse reactions that led to treatment discontinuation were: myalgia (0.3% rosuvastatin, 0.2% placebo), abdominal pain (0.03% rosuvastatin, 0.02% placebo) and rash (0.03% rosuvastatin, 0.03% placebo). Adverse reactions reported in ≥ 2% of patients and at a rate greater than or equal to placebo were myalgia (7.6% rosuvastatin, 6.6% placebo), constipation (3.3% rosuvastatin, 3.0% placebo) and nausea (2.4% rosuvastatin, placebo, 2.3%).

In JUPITER, there was a statistically significant increase in the frequency of diabetes mellitus reported by investigators; 2.8% of patients in the rosuvastatin group and 2.3% of patients in the placebo group (HR: 1.27, 95% CI: 1.05-1.53, p=0.015). The difference between treatment groups (rosuvastatin versus placebo) in mean HbA1c change from baseline was approximately 0.1%.

Pediatric Patients with Heterozygous Familial Hypercholesterolemia:
In a double blind, randomized, multi-center, placebo-controlled, 12-week study, 176 (97 male and 79 female) children and adolescents with heterozygous familial hypercholesterolemia were randomized to rosuvastatin 5, 10 or 20 mg or placebo daily. Patients ranged in age from 10 to 17 years (median age of 14 years) with approximately 30% of the patients 10 to 13 years and approximately 17%, 18%, 40%, and 25% at Tanner stages II, III, IV, and V, respectively. Females were at least 1 year post-menarche. Mean LDL-C at baseline was 233 mg/dL (range of 129 to 399). The 12-week double-blind phase was followed by a 40-week open-label dose-titration phase, where all patients (n=173) received 5 mg, 10 mg or 20 mg rosuvastatin daily.

Rosuvastatin significantly reduced LDL-C (primary end point), total cholesterol and ApoB levels at each dose compared to placebo. Results are shown in Table 8 below.

Table 8: Lipid-modifying effects of rosuvastatin in pediatric patients 10 to 17 years of age with heterozygous familial hypercholesterolemia (least-squares mean percent change from baseline to week 12)

Dose (mg)	N	LDL-C	HDL-C	Total-C	TG[a]	ApoB
Placebo	46	-1%	+7%	0%	-7%	-2%
5	42	-38%	+4%[b]	-30%	-13%[b]	-32%
10	44	-45%	+11%[b]	-34%	-15%[b]	-38%
20	44	-50%	+9%[b]	-39%	-16%[b]	-41%

a Median percent change
b Difference from placebo not statistically significant

At the end of the 12-week, double-blind treatment period, the percentage of patients achieving the LDL-C goal of less than 110 mg/dL (2.8 mmol/L) was 0% for placebo, 12% for rosuvastatin 5 mg, 41% for rosuvastatin 10 mg and 41% for rosuvastatin 20 mg. For the 40-week, open-label phase, 71% of the patients were titrated to the maximum dose of 20 mg and 41% of the patients achieved the LDL-C goal of 110 mg/dL.

The long-term efficacy of rosuvastatin therapy initiated in childhood to reduce morbidity and mortality in adulthood has not been established.

PHARMACOKINETIC PROPERTIES

Absorption: In clinical pharmacology studies in man, peak plasma concentrations of rosuvastatin were reached 3 to 5 hours following oral dosing. Both peak concentration (Cmax) and area under the plasma concentration-time curve (AUC) increased in approximate proportion to rosuvastatin dose. The absolute bioavailability of rosuvastatin is approximately 20%.

Administration of rosuvastatin with food decreased the rate of drug absorption by 20% as assessed by Cmax, but there was no effect on the extent of absorption as assessed by AUC.

Plasma concentrations of rosuvastatin do not differ following evening or morning drug administration.

Significant LDL-C reductions are seen when rosuvastatin is given with or without food, and regardless of the time of day of drug administration.

Distribution: Mean volume of distribution at steady-state of rosuvastatin is approximately 134 litres. Rosuvastatin is 88% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentrations.

Metabolism: Rosuvastatin is not extensively metabolised; approximately 10% of a radio-labelled dose is recovered as metabolite. The major metabolite is N-desmethyl rosuvastatin, which is formed principally by cytochrome P450 2C9, and *in vitro* studies have demonstrated that N-desmethyl rosuvastatin has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of rosuvastatin. Overall, greater than 90% of active plasma HMG-CoA reductase inhibitory activity is accounted for by rosuvastatin.

Excretion: Following oral administration, rosuvastatin and its metabolite are primarily excreted in the faeces (90%). The elimination half-life (t½) of rosuvastatin is approximately 19 hours.

After an intravenous dose, approximately 28% of total body clearance was via the renal route and 72% by the hepatic route.

Special populations:
Age and sex: There was no clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin.

Pediatric use: The safety and effectiveness of Rosuvastatin Calcium in patients 10 to 17 years of age with heterozygous familial hypercholesterolemia were evaluated in a controlled clinical trial of 12 weeks duration followed by 40 weeks of open-label exposure. Patients treated with 5 mg, 10 mg and 20 mg daily Rosuvastatin Calcium had an adverse experience profile generally similar to that of patients treated with placebo (see *Clinical Adverse Experience*). Although not all adverse reactions identified in the adult population have been observed in clinical trials of children and adolescent patients, the same warnings and precautions for adults should be considered for children and adolescents. There was no detectable effect of Rosuvastatin Calcium on growth, weight, BMI (body mass index), or sexual maturation (see *Clinical Efficacy*) in pediatric patients (10 to 17 years of age). Adolescent females should be counseled on appropriate contraceptive methods while on Rosuvastatin Calcium therapy (see *Pharmacokinetic - Special Populations*). Rosuvastatin Calcium has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age. Doses of Rosuvastatin Calcium greater than 20 mg have not been studied in the pediatric population.

In children and adolescents with homozygous familial hypercholesterolemia experience is limited to eight patients (aged 8 years and above).

In a pharmacokinetic study, 18 patients (9 boys and 9 girls) 10 to 17 years of age with heterozygous FH received single and multiple oral doses of Rosuvastatin Calcium. Both Cmax and AUC of rosuvastatin were similar to values observed in adult subjects administered the same doses.

Genetic polymorphisms: Disposition of HMG-CoA reductase inhibitors, including rosuvastatin, involves OATP1B1 and BCRP transporter proteins. In patients with SLCO1B1 (OATP1B1) and/or ABCG2 (BCRP) genetic polymorphisms there is a risk of increased rosuvastatin exposure. Individual polymorphisms of SLCO1B1 c.521CC and ABCG2 c.421AA are associated with an approximate 1.6-fold higher rosuvastatin exposure (AUC) compared to the SLCO1B1 c.521TT or ABCG2 c.421CC 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 Calcium is recommended.

Race: Pharmacokinetic studies show an approximate 2-fold elevation in median AUC in Asian subjects compared with Caucasians. A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic and Black or Afro-Caribbean groups.

Patients with renal impairment: Mild to moderate renal impairment (CLcr ≥30 mL/min/1.73 m^2) had no influence on plasma concentrations of rosuvastatin. However, plasma concentrations of rosuvastatin increased to a clinically significant extent (about 3-fold) in patients with severe renal impairment (CLcr <30 mL/min/1.73 m^2) not receiving hemodialysis compared with healthy subjects (CLcr >80 mL/min/1.73 m^2).

PHARMACEUTICAL PARTICULARS

List of excipients

Rosuvastatin Calcium
Anhydrous Lactose
Microcrystalline Cellulose
Crospovidone
Light Magnesium Oxide
Magnesium stearate

Film coating:
Crescord 5:
Hypromellose
Lactose monohydrate
Triacetin
Titanium dioxide
Ferric oxide yellow

Crescord 10 and 20:
Hypromellose
Triacetin
Titanium dioxide
Lactose monohydrate
Iron oxide red
Quinoline Yellow Aluminum Lake
Brilliant blue FCF Aluminum Lake

STORAGE CONDITIONS

Store below 30°C. Protect from moisture.

DOSAGE FORMS AND PACKAGING AVAILABLE

CRESCORD 5, 10, 20 is available in 3 x 10 tablets Aluminium-Aluminium blister pack.

NAME AND ADDRESS OF MANUFACTURER

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DATE OF REVISION OF PI

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