PRODUCT MONOGRAPH

[Pr]APO-ROSUVASTATIN

Rosuvastatin Calcium Tablets, USP

5 mg, 10 mg, 20 mg and 40 mg rosuvastatin (as rosuvastatin calcium)

LIPID METABOLISM REGULATOR

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablets / 5 mg, 10 mg, 20 mg and 40 mg	Colloidal silicon dioxide NF, crospovidone NF, ferric oxide red NF (10 mg, 20 mg & 40 mg tablets only), ferric oxide yellow NF (5 mg only), hydroxypropyl cellulose NF, hydroxypropyl methylcellulose USP, lactose monohydrate NF, magnesium stearate NF, microcrystalline cellulose NF, polyethylene glycol NF, titanium dioxide USP.

INDICATIONS AND CLINICAL USE

Hypercholesterolemia

Adults

APO-ROSUVASTATIN (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 (Total-C), LDL-C, ApoB, the Total-C/HDL-C ratio and triglycerides (TG) and for increasing HDL-C; in hyperlipidemic and dyslipidemic conditions, when response to diet and exercise alone has been inadequate including:

- Primary hypercholesterolemia (Type IIa including severe non-familial hypercholesterolemia)
- Combined (mixed) dyslipidemia (Type IIb)
- Homozygous familial hypercholesterolemia where APO-ROSUVASTATIN is used either alone or as an adjunct to diet and other lipid lowering treatments such as apheresis.

CONTRAINDICATIONS

APO-ROSUVASTATIN (rosuvastatin calcium) is contraindicated:

- In patients who are hypersensitive to any component of this medication (see DOSAGE FORMS, COMPOSITION AND PACKAGING).

- In patients with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal (see WARNINGS AND PRECAUTIONS).

- In pregnant and nursing women.

  Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). APO-ROSUVASTATIN should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the possible harm. If the patient becomes pregnant while taking APO-ROSUVASTATIN, the drug should be discontinued immediately and the patient apprised of the potential harm to the fetus. Atherosclerosis being a chronic process, discontinuation of lipid metabolism regulating drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women, Nursing Women).

- In patients using concomitant cyclosporine (see DRUG INTERACTIONS).

- In patients using concomitant sofosbuvir/velpatasvir/voxilaprevir (see DRUG INTERACTIONS).

APO-ROSUVASTATIN 40 mg is contraindicated in:

- Asian patients

- Patients with pre-disposing factors for myopathy/rhabdomyolysis such as:

  - Personal or family history of hereditary muscular disorders

  - Previous history of muscle toxicity with another 3-Hydroxyl-3-Methylglutaryl-Coenzyme A (HMG-CoA) reductase inhibitor

  - Concomitant use of a fibrate or niacin

  - Severe hepatic impairment

  - Severe renal impairment (CrCl < 30 mL/min/1.73 m^2) (see DOSAGE AND ADMINISTRATION, Patients with Renal Impairment)

  - Hypothyroidism

  - Alcohol abuse

  - Situations where an increase in rosuvastatin plasma levels may occur (see WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS, DOSAGE AND

ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

WARNINGS AND PRECAUTIONS

General

Before instituting therapy with APO-ROSUVASTATIN (rosuvastatin calcium), an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, weight reduction in overweight patients and to treat other underlying medical problems and associated cardiovascular risk factors. The patient should be advised to inform subsequent physicians of the prior use of APO-ROSUVASTATIN or any other lipid-lowering agent.

Cardiovascular

Co-enzyme Q_{10} (ubiquinone)

Ubiquinone levels were not measured in rosuvastatin calcium clinical trials. Significant decreases in circulating ubiquinone levels in patients treated with other statins have been observed. The clinical significance of a potential long-term statin-induced deficiency of ubiquinone has not been established. It has been reported that a decrease in myocardial ubiquinone levels could lead to impaired cardiac function in patients with borderline congestive heart failure (see REFERENCES).

Endocrine and Metabolism

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Rosuvastatin demonstrated no effect upon nonstimulated cortisol levels and no effect on thyroid metabolism as assessed by TSH plasma concentration. In rosuvastatin calcium treated patients, there was no impairment of adrenocortical reserve and no reduction in plasma cortisol concentrations. Clinical studies with other HMG-CoA reductase inhibitors have suggested that these agents do not reduce plasma testosterone concentration. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown.

Patients treated with rosuvastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients receiving other drugs (e.g. ketoconazole, spironolactone or cimetidine) that may decrease the levels of endogenous steroid hormones.

Plasma Glucose

Increases in fasting glucose and HbA1c levels have been reported with inhibitors of HMG-CoA reductase as a class. For some patients, at high risk of diabetes mellitus, hyperglycemia was sufficient to shift them to the diabetes status. The benefit of treatment continues to outweigh the small increased risk. Periodic monitoring of these patients is recommended.

In the JUPITER trial, rosuvastatin 20 mg was observed to increase plasma glucose levels, which were sufficient to shift some prediabetic subjects to the diabetes mellitus status (see ADVERSE REACTIONS).

Lipoprotein(a)

In some patients, the beneficial effect of lowered total cholesterol and LDL-C levels may be partly blunted by a concomitant increase in the Lipoprotein(a) [Lp(a)] concentrations. Present knowledge suggests the importance of high Lp(a) levels as an emerging risk factor for coronary heart disease. It is thus desirable to maintain and reinforce lifestyle changes in high risk patients placed on rosuvastatin therapy.

Hepatic/Biliary/Pancreatic

Hepatic Effects

APO-ROSUVASTATIN is contraindicated in patients with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal.

As with other HMG-CoA reductase inhibitors, it is recommended that a liver function test be carried out prior to, and 3 months following, the initiation of APO-ROSUVASTATIN or if the patient is titrated to the dose of 40 mg. APO-ROSUVASTATIN should be discontinued or the dose reduced if the level of transaminases is greater than 3 times the upper limit of normal.

APO-ROSUVASTATIN, as well as other HMG-CoA reductase inhibitors should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease.

As with other HMG-CoA reductase inhibitors, a dose-related increase in transaminases has been observed in a small number of patients taking rosuvastatin (< 0.5%); the majority of cases were mild, asymptomatic and transient.

There have been rare post-marketing reports of fatal and non-fatal hepatic failure in patients taking statins, including rosuvastatin (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions). If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with APO-ROSUVASTATIN, promptly interrupt therapy. If an alternate etiology is not found, do not restart APO-ROSUVASTATIN.

Hepatic Impairment

In subjects with varying degrees of hepatic impairment there was no evidence of increased exposure to rosuvastatin other than in 2 subjects with the most severe liver disease (Child-Pugh scores of 8 and 9). In these subjects, systemic exposure was increased by at least 2-fold compared to subjects with lower Child-Pugh scores (see DOSAGE AND ADMINISTRATION, Patients with Hepatic Impairment).

Muscle Effects

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with rosuvastatin calcium and with other HMG-CoA reductase inhibitors.

Effects on skeletal muscle such as myalgia, myopathy and, rarely, rhabdomyolysis have been reported in patients treated with rosuvastatin calcium at all doses and in particular with the 40 mg dose.

Myopathy, defined as muscle pain or muscle weakness in conjunction with increases in creatine kinase (CK) values to greater than ten times the upper limit of normal, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness and/or marked elevation of CK. Patients should be advised to report promptly any unexplained muscle pain, tenderness or weakness, particularly if associated with malaise or fever. Patients who develop any signs or symptoms suggestive of myopathy should have their CK levels measured. APO-ROSUVASTATIN therapy should be discontinued if markedly elevated CK levels (> 10 x ULN) are measured or myopathy is diagnosed or suspected.

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy associated with statin use. IMNM is characterized by:

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

Pre-disposing Factors for Myopathy/Rhabdomyolysis

APO-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:

- Personal or family history of hereditary muscular disorders
- Previous history of muscle toxicity with another HMG-CoA reductase inhibitor
- Concomitant use of a fibrate or niacin
- Hypothyroidism
- Alcohol abuse
- Excessive physical exercise

- Age > 70 years
- Renal impairment
- Hepatic impairment
- Diabetes with hepatic fatty change
- Surgery and trauma
- Frailty
- Situations where an increase in plasma levels of rosuvastatin may occur (see CONTRAINDICATIONS, DRUG INTERACTIONS, DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

In rosuvastatin calcium trials there was no evidence of increased skeletal muscle effects when rosuvastatin calcium was dosed with concomitant therapy such as fibric acid derivatives (including fenofibrate and gemfibrozil), nicotinic acid, azole antifungals and macrolide antibiotics. However, an increase in the incidence of myositis and myopathy has been seen in patients receiving other HMG-CoA reductase inhibitors together with these medicines.

APO-ROSUVASTATIN therapy should be temporarily withheld or discontinued in any patient with an acute serious condition suggestive of myopathy or predisposing to the development of rhabdomyolysis (e.g. sepsis, hypotension, major surgery, trauma, severe metabolic endocrine and electrolyte disorders, or uncontrolled seizures).

Renal

Renal Impairment

Subjects with severe renal impairment (CrCl < 30 mL/min/l.73m^2) had a 3-fold increase in plasma concentration of rosuvastatin compared to healthy volunteers and, therefore, APO-ROSUVASTATIN 40 mg is contraindicated in these patients (see CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION, Patients with Renal Impairment).

In subjects with varying degrees of renal impairment, mild to moderate renal disease had little influence on plasma concentrations of rosuvastatin.

During the clinical development program, dipstick-positive proteinuria and microscopic hematuria were observed among rosuvastatin-treated patients, predominantly in patients dosed above the recommended dose range (i.e. 80 mg). Abnormal urinalysis testing (dipstick-positive proteinuria) has been seen in patients taking rosuvastatin calcium and other HMG-CoA reductase inhibitors. This finding was more frequent in patients taking 40 mg when compared to lower doses of rosuvastatin or comparator statins. Shifts in urine protein from none or trace to ++ (dipstick) 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. The protein detected was mostly tubular in origin. In most cases, proteinuria was generally transient and it decreased or disappeared spontaneously on continued therapy. It has not been shown to be predictive of acute or progressive renal disease.

Nevertheless, a dose reduction may be considered for patients with unexplained persistent proteinuria during routine testing.

Sensitivity/Resistance

Hypersensitivity

An apparent hypersensitivity syndrome has been reported rarely with other HMG-CoA reductase inhibitors. This has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive antinuclear antibody (ANA), erythrocyte sedimentation rate (ESR) increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis and erythema multiforme including Stevens-Johnson syndrome. Treatment should be discontinued if hypersensitivity is suspected (see CONTRAINDICATIONS).

Special Populations

Pregnant Women:

APO-ROSUVASTATIN is contraindicated during pregnancy (see CONTRAINDICATIONS).

Nursing Women:

It is not known whether rosuvastatin is excreted in human milk. Because of the potential for adverse reactions in nursing infants, women taking APO-ROSUVASTATIN should not breast-feed (see CONTRAINDICATIONS).

APO-ROSUVASTATIN is not for use in children and adolescent less than 18 years of age.

Geriatrics (≥ 65 years of age):

There were no clinically significant pharmacokinetic differences between young and elderly patients (≥ 65 years) (see DOSAGE AND ADMINISTRATION, Use in Elderly). However, elderly patients may be more susceptible to myopathy (see WARNINGS AND PRECAUTIONS, Muscle Effects, Pre-disposing Factors for Myopathy/Rhabdomyolysis).

Race:

Results of pharmacokinetic studies, including a large study conducted in North America, have demonstrated an approximate 2-fold elevation in median exposure in Asian subjects (having either Filipino, Chinese, Japanese, Korean, Vietnamese or Asian-Indian origin) when compared with a Caucasian control group. This increase should be considered when making rosuvastatin dosing decisions for Asian patients and the dose of 40 mg is contraindicated in these patients (see

ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions, CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION, Race).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Rosuvastatin calcium is generally well tolerated. The adverse events seen with rosuvastatin calcium are generally mild and transient.

Rosuvastatin calcium clinical trial experience is extensive, involving 9800 patients treated with rosuvastatin calcium in placebo controlled trials and 9855 patients treated with rosuvastatin calcium in active controlled clinical trials. Discontinuation of therapy due to adverse events occurred in 2.6% of patients receiving rosuvastatin calcium and 1.8% of patients receiving placebo. The most frequently reported adverse events at an incidence ≥ 1% and at a rate greater than placebo were arthralgia, upper abdominal pain and ALT increase. Adverse events observed or reported in short- and long-term trials are as follows.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adults

Short-term Controlled Trials

Short-term controlled trials involved 1290 patients within placebo-controlled trials of 6 to 16 weeks' duration (768 of which were treated with rosuvastatin) and 11641 patients within placebo and active controlled clinical trials of 6 to 52 weeks duration (5319 of which were treated with rosuvastatin). In all controlled clinical trials, 3.2% of patients were withdrawn from rosuvastatin calcium therapy due to adverse events. This withdrawal rate was comparable to that reported in placebo-controlled studies.

Associated adverse events occurring at an incidence ≥ 1% in patients participating in placebo-controlled clinical studies of rosuvastatin, are shown in Table 1.

Table 1 Number (%) of Subjects with Associated Adverse Events Occurring with ≥1% Incidence in any Treatment Group: Placebo Controlled Pool

Body System/ Adverse Event	Placebo (%) (N=367)	Total Rosuvastatin (%) (N=768)
Whole Body		

Body System/ Adverse Event	Placebo (%) (N=367)	Total Rosuvastatin (%) (N=768)
Abdominal pain	2.2	1.7
Asthenia	0.5	1.3
Headache	2.2	1.4
Digestive		
Constipation	1.4	1.0
Diarrhea	1.6	1.3
Dyspepsia	1.9	0.7
Flatulence	2.7	1.8
Nausea	1.6	2.2
Musculoskeletal		
Myalgia	0.5	1.6
Nervous System		
Dizziness	1.6	0.5
Insomnia	1.9	0.4

Long-term Controlled Morbidity and Mortality Trials

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 involving 17,802 participants treated with rosuvastatin calcium 20 mg once daily (n=8901) or placebo (n=8901), rosuvastatin calcium 20 mg was generally well tolerated. Subjects were followed for a mean duration of 2 years.

Discontinuation of therapy due to an adverse event occurred in 5.6% of subjects treated with rosuvastatin calcium and 5.5% of subjects treated with placebo. The most common adverse events that led to discontinuation from the study were: myalgia, arthralgia, abdominal pain and constipation. The associated adverse reaction reported in ≥ 1% of patients and at a rate greater than or equal to placebo was myalgia (2.4% rosuvastatin calcium, 2.0% placebo.)

Treatment emergent adverse events regardless of causality occurring at an incidence ≥ 1% and at a rate greater than placebo in patients participating in the JUPITER trial are shown in Table 2.

Table 2 Number (%) of Subjects with Treatment Emergent Adverse Events Regardless of Causality Occurring with ≥ 1% Incidence and > than Placebo: JUPITER

Body System/ Adverse Event	Placebo (%) (N=8901)	Total Rosuvastatin 20 mg (%) (N = 8901)
Blood		
Anemia	2.1	2.2
Cardiac		
Palpitations	0.9	1.0
Gastrointestinal		
Diarrhea	4.6	4.7
Constipation	3.0	3.3
Nausea	2.3	2.4

Body System/ Adverse Event	Placebo (%) (N=8901)	Total Rosuvastatin 20 mg (%) (N = 8901)
General disorders		
Edema peripheral	3.0	3.7
Fatigue	3.5	3.7
Hepatobiliary		
Cholelithiasis	0.9	1.0
Infections		
Urinary tract	8.6	8.7
Nasopharyngitis	7.2	7.6
Bronchitis	7.1	7.2
Sinusitis	3.7	4.0
Influenza	3.6	4.0
Lower Respiratory tract	2.7	2.9
Gastroenteritis	1.7	1.9
Herpes zoster	1.4	1.6
Injury		
Contusion	1.4	1.7
Investigation		
ALT increased	1.0	1.4
Blood glucose increased	0.7	1.0
Metabolism		
Diabetes mellitus	2.5	3.0
Musculoskeletal		
Back pain	6.9	7.6
Myalgia	6.6	7.6
Arthritis	5.6	5.8
Arthralgia	3.2	3.8
Muscle spasms	3.2	3.6
Osteoarthritis	1.4	1.8
Bursitis	1.3	1.5
Neck Pain	1.0	1.1
Osteoporosis	0.8	1.0
Neoplasms		
Basal cell carcinoma	0.9	1.0
Psychiatric		
Insomnia	2.3	2.5
Renal		
Hematuria	2.0	2.4
Proteinuria	1.3	1.4
Respiratory		
Epistaxis	0.8	1.0

Less Common Clinical Trial Adverse Drug Reactions (< 1%)

The frequency of adverse events in all clinical trials and considered possibly, probably or

definitely drug related are as follows:

Uncommon (≥ 0.1% and < 1%):	Pruritus, rash, urticaria, arthralgia, muscle weakness, arthritis, constipation, nausea, dyspepsia, gastroesophageal reflux disease, ALT increase, creatine phosphokinase increase, hepatic enzyme increase, creatinine increase, paraesthesia, tremor, general pain, proteinuria, sinusitis, insomnia, abnormal hepatic function, vertigo, diabetes mellitus.
Rare (≥ 0.01% and < 0.1%):	Myopathy (including myositis), rhabdomyolysis and hypersensitivity reactions including angioedema.

The following additional adverse events were reported in controlled clinical trials, regardless of causality:

Accidental injury, back and chest pain, flu syndrome, infection, urinary tract infection, diarrhea, flatulence, gastroenteritis, hypertonia, bronchitis, increased cough, rhinitis and pharyngitis.

In long-term controlled clinical trials rosuvastatin calcium was shown to have no harmful effect on the ocular lens.

Abnormal Hematologic and Clinical Chemistry Findings

As with other HMG-CoA reductase inhibitors, a dose-related increase in liver transaminases and CK has been observed in a small number of patients taking rosuvastatin (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

Abnormal urinalysis testing (dipstick-positive proteinuria) has been seen in a small number of patients taking rosuvastatin calcium and other HMG-CoA reductase inhibitors. The protein detected was mostly tubular in origin. In most cases, proteinuria decreases or disappears spontaneously on continued therapy and is not predictive of acute or progressive renal disease (see WARNINGS AND PRECAUTIONS, Renal).

In the JUPITER trial, occurrences of diabetes mellitus as a pre-specified secondary outcome were reported more frequently in the rosuvastatin calcium-treated patients (2.8%) than in placebo (2.3%) and a slight increase in the number of subjects whose fasting glucose levels increased to ≥ 7.0 mmol/L (126 mg/dL) was observed in subjects treated with rosuvastatin calcium who were primarily already at high risk for developing diabetes. There was a 0.1% increase in mean HbA1c with rosuvastatin calcium compared to placebo. A causal relationship with statins and diabetes mellitus has not been definitely established.

Post-Market Adverse Drug Reactions

Because post-market reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug

exposure. In addition to the events reported above, the following adverse events have been reported during post-marketing experience with rosuvastatin calcium, regardless of causality assessment.

Skeletal muscle effects: Very rare: arthralgia, immune-mediated necrotizing myopathy

It has been observed that as with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis in post-marketing use is higher at the highest marketed dose (see WARNINGS AND PRECAUTIONS, Muscle Effects).

Hematological disorders: Thrombocytopenia has been reported with rosuvastatin calcium.

Hepatobiliary disorders: Very rare: jaundice, hepatitis

Nervous system disorders: Very rare: memory loss; frequency unknown: peripheral neuropathy

Endocrine disorders: Increases in fasting glucose and HbA1c levels have been reported with rosuvastatin calcium.

Other: Rare: pancreatitis; Very rare: gynecomastia

The following adverse events have been reported with some statins:

Sleep Disturbances, including insomnia and nightmares.

Mood related disorders including depression.

Fatal and non-fatal hepatic failure.

Cases of erectile dysfunction have been reported in association with the use of statins.

Interstitial lung disease: very rare cases of interstitial lung disease, especially with long term therapy. If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

There have been rare post-marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive 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 of 3 weeks).

DRUG INTERACTIONS

Overview

In rosuvastatin calcium clinical trials there was no evidence of increased skeletal muscle effects when rosuvastatin was dosed with any concomitant therapy. However, rosuvastatin calcium and other HMG-CoA reductase inhibitors may cause dose-related increases in serum transaminases and CK levels. An increase in the incidence of myositis and myopathy has been seen in patients receiving other HMG-CoA reductase inhibitors with cyclosporine, fibric acid derivatives (including gemfibrozil), nicotinic acid, azole antifungals and macrolide antibiotics.

Cytochrome P450 Inhibitors

In vitro and *in vivo* data indicate that rosuvastatin has no clinically significant cytochrome P450 interactions (as substrate, inhibitor or inducer). Consequently, there is little potential for drug-drug interactions upon coadministration with agents that are metabolised by cytochrome P450. Rosuvastatin clearance is not dependent on metabolism by cytochrome P450 3A4 to a clinically significant extent. This has been confirmed in studies with known cytochrome P450 2C9, 2C19 and 3A inhibitors (ketoconazole, fluconazole).

Protease Inhibitors

Coadministration of rosuvastatin with certain protease inhibitors may increase the rosuvastatin exposure, (AUC) up to 7-fold (see Table 3). Stop using APO-ROSUVASTATIN or dose adjust depending on the level of effect on rosuvastatin exposure (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Transporter Protein Inhibitors

Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter OATP1B1 and efflux transporter BCRP. Concomitant administration of APO-ROSUVASTATIN with medicines that are inhibitors of these transporter proteins may result in increased rosuvastatin plasma concentrations and an increased risk of myopathy (see WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION, Dosing Considerations in Special Populations and DRUG INTERACTIONS, Drug-Drug Interactions (Table 3)).

Concomitant Therapy with Other Lipid Metabolism Regulators

Coadministration of fenofibrate and rosuvastatin calcium 10 mg did not lead to a clinically significant change in the plasma concentrations of either drug. In addition, neither myopathy nor marked CK elevations (>10 x ULN) were observed in a study of 128 patients who received rosuvastatin calcium 10, 20 and 40 mg plus extended-release niacin or in a second study of 103 patients who received rosuvastatin calcium 5 and 10 mg plus fenofibrate. Based on the above data, no pharmacokinetic or pharmacodynamic interaction was observed. No data is available with other fibrates.

Based on post-marketing surveillance, gemfibrozil, fenofibrate, other fibrates and lipid lowering doses of niacin (nicotinic acid) may increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given

alone (see WARNINGS AND PRECAUTIONS, Muscle Effects, Pre-disposing Factors for Myopathy/Rhabdomyolysis). Therefore, combined drug therapy should be approached with caution.

Concomitant Therapies without Clinically Significant Interactions

Bile Acid Sequestrants: APO-ROSUVASTATIN can be used in combination with bile acid sequestrant (e.g. cholestyramine).

Ezetimibe: Coadministration of ezetimibe with rosuvastatin calcium resulted in a 19% increase in the AUC of rosuvastatin. This small increase is not considered clinically significant.

Ketoconazole: Coadministration of ketoconazole with rosuvastatin calcium resulted in no change in plasma concentrations of rosuvastatin.

Erythromycin: Coadministration of erythromycin with rosuvastatin calcium resulted in small decreases in plasma concentrations of rosuvastatin. These reductions were not considered clinically significant.

Fluconazole: Coadministration of fluconazole with rosuvastatin calcium resulted in a 14% increase in the AUC of rosuvastatin. This small increase is not considered clinically significant.

Fosamprenavir: Coadministration of fosamprenavir 700 mg /ritonavir 100 mg (BID, 8 days) with rosuvastatin calcium 10 mg (single dose) resulted in no clinically significant effect on the AUC of rosuvastatin.

Digoxin: Coadministration of digoxin and rosuvastatin calcium did not lead to any clinically significant interactions.

Rifampin: Coadministration of rifampin with rosuvastatin calcium resulted in no change in plasma concentrations of rosuvastatin.

Other Drugs: Although specific interaction studies were not performed, rosuvastatin calcium has been studied in over 5300 patients in clinical trials. Many patients were receiving a variety of medications including antihypertensive agents (beta-adrenergic blocking agents, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and diuretics), antidiabetic agents (biguanides, sulfonylureas, alpha glucosidase inhibitors and thiazolidinediones), and hormone replacement therapy without evidence of clinically significant adverse interactions.

Drug-Drug Interactions

The drugs listed in Table 3 are based on either drug interaction case reports or studies or potential interactions due to the expected magnitude and seriousness of the interaction (i.e. those identified as contraindicated).

Table 3 Established or Potential Drug-Drug Interactions

Proper Name	Effect	Clinical Comment
Immunosuppressants (Including Cyclosporine)	Rosuvastatin calcium 10 and 20 mg were administered to cardiac transplant patients (at least 6 months post-transplant) whose concomitant medication included cyclosporine, prednisone and azathioprine. Results showed that cyclosporine pharmacokinetics were not affected by rosuvastatin. However, cyclosporine did increase the systemic exposure of rosuvastatin by 11-fold (C_{max}) and 7.1-fold ($AUC_{[0-24]}$) compared with historical data in healthy individuals.	The concomitant use of APO-ROSUVASTATIN and cyclosporine is contraindicated (see CONTRAINDICATIONS).
Darolutamide	Coadministration of rosuvastatin calcium 5 mg (single dose) with darolutamide 600 mg BID, 5 days; approximately a 5.2-fold increase in rosuvastatin AUC and 5-fold increase in rosuvastatin C_{max}.	For coadministration, the dose of APO-ROSUVASTATIN should not exceed 5 mg once daily.
Regorafenib	Coadministration of rosuvastatin calcium 5 mg (single dose) with regorafenib 160 mg OD, 14 days; approximately a 3.8-fold increase in rosuvastatin AUC and 4.6-fold increase in rosuvastatin C_{max}.	For coadministration, the dose of APO-ROSUVASTATIN should not exceed 10 mg daily.
Protease Inhibitors	Coadministration of rosuvastatin calcium with various protease inhibitors, including several in combination with ritonavir, to healthy volunteers resulted in the following changes to rosuvastatin plasma levels: Atazanavir 300 mg/ritonavir 100 mg (OD, 8 days), rosuvastatin calcium 10 mg (single dose); approximately a 3.1-fold increase in rosuvastatin mean $AUC_{(0-24)}$ Lopinavir 400 mg/ritonavir 100 mg (BID, 17 days), rosuvastatin calcium 20 mg (OD, 7 days); approximately a 2.1-fold increase in rosuvastatin mean $AUC_{(0-24)}$ Ombitasvir 25 mg/paritaprevir 150 mg/ritonavir 100 mg/dasabuvir 400 mg BID, rosuvastatin calcium 5 mg (single dose); approximately 7.13-fold and 2.59-fold respective increases for C_{max} and AUC	For coadministration with atazanavir /ritonavir, the dose of APO-ROSUVASTATIN should not exceed 10 mg daily. For coadministration with lopinavir/ritonavir, darunavir/ritonavir or tipranavir/ritonavir, the dose of APO-ROSUVASTATIN should not exceed 20 mg daily. For coadministration, the dose of APO-ROSUVASTATIN should not exceed 10 mg daily in combination with 3D treatment and 20 mg daily for combination with 2D treatment.

Proper Name	Effect	Clinical Comment
	in three direct-acting antiviral agents (3D) and 2.61-fold and 1.32-fold increases for C_{max} and AUC in two direct-acting antiviral agents (2D) treatment.	
	Simeprevir 150 mg (OD, 7 days), rosuvastatin calcium 10 mg (single dose); approximately a 3.2-fold increase in rosuvastatin C_{max} and 2.8-fold increase in rosuvastatin AUC.	For coadministration, the dose of APO-ROSUVASTATIN should not exceed 10 mg daily.
	Sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg + voxilaprevir 100 mg (OD, 15 days), rosuvastatin calcium 10 mg (single dose); approximately a 7.39-fold increase in rosuvastatin AUC.	The concomitant use of APO-ROSUVASTATIN with sofosbuvir/velpatasvir/ voxilaprevir is contraindicated (see CONTRAINDICATIONS).
	Velpatasvir 100 mg OD, rosuvastatin calcium 10 mg (single dose); approximately 2.69-fold increase in rosuvastatin AUC.	For coadministration, the dose of APO-ROSUVASTATIN should not exceed 10 mg daily.
	Grazoprevir 200 mg OD, rosuvastatin calcium 10 mg (single dose); approximately 1.85-fold increase in rosuvastatin AUC; Grazoprevir 200 mg/elbasvir 50 mg OD, rosuvastatin calcium 10 mg (single dose); approximately 2.26-fold increase in rosuvastatin AUC.	For coadministration, the dose of APO-ROSUVASTATIN should not exceed 10 mg daily with grazoprevir/elbasvir and 20 mg daily with grazoprevir alone.
	Glecaprevir 400 mg/pibrentasvir 120 mg (OD, 7 days), rosuvastatin calcium 5 mg OD; approximately 2.2-fold increase in rosuvastatin AUC.	For coadministration, the dose of APO-ROSUVASTATIN should not exceed 10 mg daily.
Clopidogrel	Coadministration of rosuvastatin calcium 20 mg (single dose) with clopidogrel 300 mg loading, followed by 75 mg at 24 hours resulted in approximately a 2-fold increase in the mean AUC of rosuvastatin.	The dose of APO-ROSUVASTATIN should not exceed 20 mg daily when used concomitantly with clopidogrel.
Protease Inhibitors	Darunavir 600 mg/ritonavir 100 mg (BID, 7 days), rosuvastatin calcium 10 mg (OD, 7 days); approximately a 1.5-fold increase in rosuvastatin mean $AUC_{(0-24)}$	For coadministration with darunavir/ritonavir or tipranavir/ritonavir the dose of APO-ROSUVASTATIN should not exceed 20 mg daily.
	Tipranavir 500 mg/ritonavir 200 mg (BID, 11 days), rosuvastatin calcium 10 mg (single dose); approximately a 1.4-fold	

Proper Name	Effect	Clinical Comment
	increase in rosuvastatin mean $AUC_{(0-24)}$	
Gemfibrozil	Coadministration of a single rosuvastatin dose (80 mg) to healthy volunteers on gemfibrozil (600 mg bid) resulted in a 2.2 and 1.9-fold increase in mean C_{max} and mean AUC of rosuvastatin respectively.	Due to an observed increased risk of myopathy/ rhabdomyolysis, combination therapy with APO-ROSUVASTATIN and gemfibrozil should be avoided. If used together, the dose of APO-ROSUVASTATIN should not exceed 20 mg once daily.
Eltrombopag	Coadministration of rosuvastatin calcium 10 mg (single dose) and eltrombopag 75 mg (OD, 5 days) to healthy volunteers resulted in approximately a 1.6-fold increase in the mean AUC of rosuvastatin	The dose of APO-ROSUVASTATIN should not exceed 20 mg daily when used concomitantly with eltrombopag.
Dronedarone	Coadministration of rosuvastatin calcium and dronedarone 400 mg (bid) resulted in approximately a 1.4-fold increase in mean AUC of rosuvastatin.	The dose of APO-ROSUVASTATIN should not exceed 20 mg daily when used concomitantly with dronedarone.
Itraconazole	Coadministration of rosuvastatin calcium 10 mg (single dose) with itraconazole 200 mg (OD, 5 days) to healthy volunteers resulted in a 1.4-fold increase in the mean AUC of rosuvastatin.	The dose of APO-ROSUVASTATIN should not exceed 20 mg daily when used concomitantly with itraconazole.
Coumarin Anticoagulants	As with other HMG-CoA reductase inhibitors, coadministration of APO-ROSUVASTATIN and coumarin (e.g. warfarin) may result in a rise in International Normalized Ratio (INR) compared to coumarin alone. In healthy subjects, the coadministration of rosuvastatin 40 mg (10 days) and warfarin 25 mg (single dose) produced a higher mean $_{max}$INR and AUC-INR than achieved with warfarin alone. Coadministration of rosuvastatin calcium 10 and 80 mg to patients on stable warfarin therapy resulted in clinically significant rises in INR (>4, baseline 2-3). The mechanism for this effect is unknown, but is likely due to a pharmacodynamic interaction with warfarin rather than a pharmacokinetic interaction as no relevant differences in the pharmacokinetics of either drug were observed.	In patients taking coumarin, monitoring of INR is recommended at initiation or cessation of therapy with rosuvastatin or following dose adjustment. Rosuvastatin therapy has not been associated with bleeding or changes in INR in patients not taking anticoagulants.
Antacids	Simultaneous dosing of rosuvastatin calcium with an antacid suspension containing aluminium and magnesium hydroxide resulted in a decrease of rosuvastatin plasma concentration by approximately 50%.	The clinical relevance of this interaction has not been studied. However, the effect was mitigated when the antacid was dosed 2 hours after rosuvastatin calcium. This interaction should not be clinically

Proper Name	Effect	Clinical Comment
		relevant in patients using this type of antacid infrequently. A frequent antacid user should be instructed to take APO-ROSUVASTATIN at a time of day when they are less likely to need the antacid.
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.	Co-administration of APO-ROSUVASTATIN with fusidic acid should be avoided. Temporary suspension of APO-ROSUVASTATIN treatment may be appropriate when the use of fusidic acid is necessary.
Oral Contraceptives	When rosuvastatin calcium 40 mg was coadministered with a representative oral contraceptive (ethinyl estradiol [35 mcg] and norgestrel [180 mcg on days 1 to 7, 215 mcg on days 8 to 15, and 250 mcg on days 16 to 21]) no reduction in contraceptive efficacy was observed. An increase in plasma concentrations (AUC) of ethinyl estradiol (26%) and norgestrel (34%) occurred.	These increased plasma levels should be considered when selecting oral contraceptive doses.

When it is necessary to coadminister APO-ROSUVASTATIN with other medicines known to increase exposure to rosuvastatin, doses of APO-ROSUVASTATIN should be adjusted. It is recommended that prescribers consult the relevant product information when considering administration of such products together with APO-ROSUVASTATIN.

If the expected increase in rosuvastatin exposure (AUC) is approximately 2-fold or higher, the starting dose of APO-ROSUVASTATIN should not exceed 5 mg once daily. The maximum daily dose of APO-ROSUVASTATIN should be adjusted so that the expected rosuvastatin exposure would not likely exceed that of a 40 mg daily dose of APO-ROSUVASTATIN taken without interacting medicines (see CONTRAINDICATIONS and DRUG INTERACTIONS, Drug-Drug Interactions (Table 3)).

Drug-Food Interactions

APO-ROSUVASTATIN can be taken with or without food (see DOSAGE AND ADMINISTRATION).

Drug-Herb Interactions

Baicalin: Coadministration of baicalin (50 mg TID, 14 days) with rosuvastatin calcium (20 mg, single dose) resulted in a 47% decrease in the AUC of rosuvastatin.

Silymarin (from milk thistle): Coadministration of silymarin (140 mg TID, 5 days) with

rosuvastatin calcium (10 mg, single dose) resulted in no change in plasma concentrations of rosuvastatin.

DOSAGE AND ADMINISTRATION

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 APO-ROSUVASTATIN (rosuvastatin calcium), and should continue on this diet during treatment with APO-ROSUVASTATIN. If appropriate, a program of weight control and physical exercise should be implemented.

Prior to initiating therapy with APO-ROSUVASTATIN, secondary causes for elevations in plasma lipid levels should be excluded. A lipid profile should also be performed.

APO-ROSUVASTATIN may be taken in the morning or evening, with or without food.

Recommended Dose and Dosage Adjustment

Adults

Hypercholesterolemia

The dose range of APO-ROSUVASTATIN is 5 to 40 mg orally once a day. The recommended starting dose of APO-ROSUVASTATIN in most patients is 10 mg orally once daily. The majority of patients are controlled at the 10 mg dose. If necessary, dose adjustment can be made at 2-4 week intervals. The maximum response is usually achieved within 2 to 4 weeks and is maintained during chronic therapy.

Initiation of therapy with APO-ROSUVASTATIN 5 mg once daily may be considered for patients requiring less aggressive LDL-C reductions or who have predisposing factors for myopathy (see WARNINGS AND PRECAUTIONS, Muscle Effects).

Patients who are switched to APO-ROSUVASTATIN from treatment with another HMG-CoA reductase inhibitor should be started on 10 mg even if they were on a high dose of the previous HMG-CoA reductase inhibitor. A switch dose of 20 mg may be considered for patients with severe hypercholesterolemia.

For patients with severe hypercholesterolemia (including those with familial hypercholesterolemia), a 20 mg start dose may be considered. These patients should be carefully followed.

A dose of 40 mg once daily should only be used in patients with severe hypercholesterolemia who do not achieve the desired effect on 20 mg and have no predisposing factors for myopathy/rhabdomyolysis (see CONTRAINDICATIONS). Consultation with a specialist is recommended when initiating APO-ROSUVASTATIN 40 mg dose.

The dosage of APO-ROSUVASTATIN should be individualized according to baseline LDL-C,

total C/HDL-C ratio and/or TG levels to achieve the recommended desired lipid values at the lowest possible dose.

Dosing Considerations in Special Populations

Patients with Hepatic Impairment:

The usual dose range applies in patients with mild to moderate hepatic impairment. Increased systemic exposure has been observed in patients with severe hepatic impairment and, therefore, in these patients the dose of APO-ROSUVASTATIN should not exceed 20 mg once daily (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Hepatic/ Biliary/Pancreatic, Hepatic Impairment).

Patients with Renal Impairment:

The usual dose range applies in patients with mild to moderate renal impairment. Increased systemic exposure to rosuvastatin has been observed in patients with severe renal impairment. For patients with severe renal impairment (creatinine clearance < 30 mL/min/l.73 m^2) the starting dose of APO-ROSUVASTATIN should be 5 mg and not exceed 10 mg once daily (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Renal, Renal Impairment).

Race:

The initial dose of APO-ROSUVASTATIN, in Asian patients, should be 5 mg once daily. The potential for increases in systemic exposure must be considered when making treatment decisions. The maximum dose should not exceed APO-ROSUVASTATIN 20 mg once daily (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Special Populations, Race).

APO-ROSUVASTATIN is not for use in children and adolescents less than 18 years of age.

Use in Elderly:

No dose adjustment is necessary in the elderly (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics).

Genetic polymorphisms:

Genotypes of SLCO1B1 (OATP1B1) c.521CC and ABCG2 (BCRP) c.421AA have been shown to be associated with an increase in rosuvastatin exposure (AUC) compared to SLCO1B1 c.521TT and ABCG2 c.421CC. For patients known to have the c.521CC or c.421AA genotype, a maximum once daily dose of 20 mg of APO-ROSUVASTATIN is recommended (see WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

Concomitant Therapy:

Rosuvastatin is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when APO-ROSUVASTATIN is administered concomitantly with certain medicines that may increase the plasma concentration of rosuvastatin due to interactions with these transporter proteins (see DRUG INTERACTIONS, Table 3).

Whenever possible, alternative medications should be considered, and if necessary, consider temporarily discontinuing APO-ROSUVASTATIN therapy. In situations where coadministration of these medicines with APO-ROSUVASTATIN is unavoidable, the benefit and the risk of concurrent treatment and APO-ROSUVASTATIN dosing adjustments should be carefully considered (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

OVERDOSAGE

There is no specific treatment in the event of overdosage. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted as required. Hemodialysis does not significantly enhance clearance of rosuvastatin.

For the management of a suspected drug overdose, contact your regional poison control centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

APO-ROSUVASTATIN (rosuvastatin calcium) is a synthetic, enantiomerically pure lipid-lowering agent. It is a selective, potent and competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyses the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in cholesterol biosynthesis.

Studies have shown that rosuvastatin calcium lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver by increasing the number of hepatic Low Density Lipoprotein (LDL) receptors on the cell-surface for enhanced uptake and catabolism of LDL. Additionally, rosuvastatin calcium inhibits the hepatic synthesis of Very Low Density Lipoprotein (VLDL), thereby reducing the total number of VLDL and LDL particles.

Pharmacodynamics

Epidemiologic, clinical and experimental studies have established that high LDL-C, low HDL-C and high plasma TG promote human atherosclerosis and are risk factors for developing cardiovascular disease. Some studies have also shown that the total-C/HDL-C ratio is the best predictor of coronary artery disease.
In contrast, increased levels of HDL-C are associated with decreased cardiovascular risk. Drug therapies that reduce levels of LDL-C or decrease TG while simultaneously increasing HDL-C have demonstrated reductions in rates of cardiovascular mortality and morbidity.

See also DETAILED PHARMACOLOGY- Human Pharmacology.

Pharmacokinetics

Absorption:

APO-ROSUVASTATIN is administered orally following which rosuvastatin, the active moiety, is rapidly absorbed, reaching peak plasma concentration 3 to 5 hours after dosing.

Both peak concentration (C_{max}) and area under the plasma concentration-time curve (AUC) increase in proportion to rosuvastatin dose. The absolute bioavailability of rosuvastatin is approximately 20% and there is no accumulation on repeated dosing. APO-ROSUVASTATIN may be given with or without food. Administration in the morning or evening did not affect the rate and extent of absorption nor the ability of rosuvastatin to reduce LDL-C.

Distribution:

Rosuvastatin undergoes first pass extraction in the liver, which is the primary site of cholesterol synthesis and LDL-C clearance. The mean volume of distribution at steady state of rosuvastatin is approximately 134 litres. Rosuvastatin is approximately 90% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentrations.

Metabolism:

Rosuvastatin is not extensively metabolised with approximately 10% of a radiolabeled dose recovered as metabolite. The major metabolite is N-desmethyl rosuvastatin, which is formed principally by cytochrome P450 2C9, and in *in vitro* studies has demonstrated to have approximately one-half the HMG-CoA reductase inhibitory activity of rosuvastatin. The parent compound accounts for greater than 87% of the circulating active HMG-CoA reductase inhibitor activity.

Excretion:

Following an oral dose, rosuvastatin and its metabolites are primarily excreted in the faeces (90%) with the remainder being excreted in the urine. Fecal recovery represents absorbed drug, metabolites in the bile, and unabsorbed drug. The elimination half-life ($t_{½}$) of rosuvastatin is approximately 19 hours and does not increase with increasing doses.

Special Populations and Conditions:

APO-ROSUVASTATIN is not for use in children and adolescents less than 18 years of age.

Race:

A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic and Black or Afro-Caribbean groups.

However, pharmacokinetic studies with rosuvastatin, including one conducted in North America, have demonstrated an approximate 2-fold elevation in median exposure (AUC and C_{max}) in Asian subjects when compared with a Caucasian control group (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Special Populations, Race and DOSAGE AND ADMINISTRATION, Race).

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 1.7-fold higher rosuvastatin exposure (AUC) or 2.4-fold higher exposure, respectively, compared to the SLCO1B1 c.521TT or ABCG2 c.421CC genotypes.

Primary dysbetalipoproteinemia (Fredrickson Type III hyperlipoproteinemia)

In a randomized, multicenter, double-blind crossover study, 32 patients (27 with ε2/ε2 genotype and 4 with apo E mutation [Arg145Cys]) with dysbetalipoproteinemia (Fredrickson type III) received rosuvastatin calcium 10 or 20 mg daily for 6 weeks. Rosuvastatin calcium 10 and 20 mg reduced non-HDL-C (primary end point) by 48% (95% CI: 45.6, 56.7) and 56% (95% CI: 48.5, 61.4), respectively. Rosuvastatin calcium 10 and 20 mg respectively, also reduced Total-C (43% and 48%), TG (40% and 43%), VLDL-C + IDL-C (47% and 56%), LDL-C (54% and 57%), Remnant Lipoprotein Cholesterol (56% and 65%), Apo E (43% and 43%) and increased HDL-C (10% and 11%). The effect of rosuvastatin calcium on morbidity and mortality in this patient population has not been studied.

STORAGE AND STABILITY

Store at room temperature 15°C to 30°C. Protect from moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms and Packaging

APO-ROSUVASTATIN 5 mg Tablets: Each yellow, round, biconvex, film-coated tablet engraved “APO” on one side and “ROS” over “5” on the other side contains rosuvastatin calcium equivalent to 5 mg rosuvastatin. Available in bottles of 90, 100 and 500 tablets and in unit dose blister packages of 30 (3 x 10) tablets.

APO-ROSUVASTATIN 10 mg Tablets: Each pink, round, biconvex, film-coated tablet engraved “APO” on one side and “ROS” over “10” on the other side contains rosuvastatin calcium equivalent to 10 mg rosuvastatin. Available in bottles of 90, 100 and 500 tablets and in unit dose blister packages of 30 (3 x 10) tablets.

APO-ROSUVASTATIN 20 mg Tablets: Each pink, round, biconvex, film-coated tablet engraved “APO” on one side and “ROS” over “20” on the other side contains rosuvastatin calcium equivalent to 20 mg rosuvastatin. Available in bottles of 90, 100 and 500 tablets and in unit dose blister packages of 30 (3 x 10) tablets.

APO-ROSUVASTATIN 40 mg Tablets: Each pink, oval, biconvex, film-coated tablet engraved “APO” on one side and “ROS40” on the other side contains rosuvastatin calcium equivalent to 40 mg rosuvastatin. Available in bottles of 90, 100 and 500 tablets and in unit dose blister packages of 30 (3 x 10) tablets.

Composition

In addition to the active ingredient, rosuvastatin calcium each tablet also contains the non-medicinal ingredients: Colloidal silicon dioxide NF, crospovidone NF, hydroxypropyl cellulose NF, ferric oxide red NF (10 mg, 20 mg & 40 mg tablets only), ferric oxide yellow NF (5 mg only), hydroxypropyl methylcellulose USP, lactose monohydrate NF, magnesium stearate NF, microcrystalline cellulose NF, polyethylene glycol NF, titanium dioxide USP.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

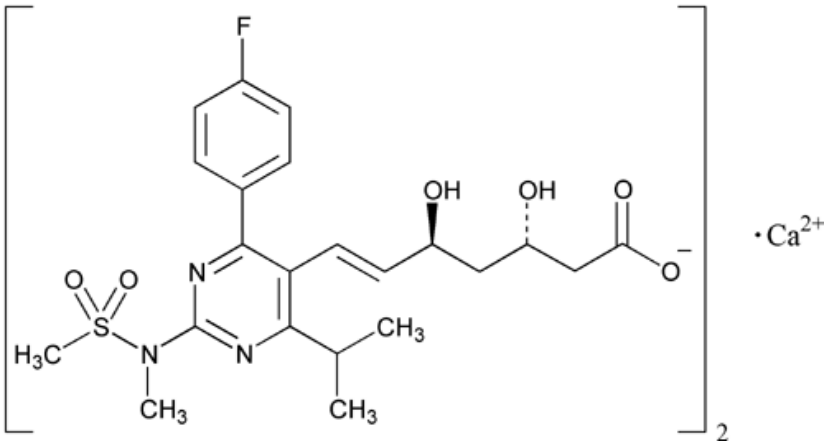
Drug Substance

Common name: Rosuvastatin calcium

Chemical name: bis [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl (methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt

Molecular formula and molecular mass: $(C_{22}H_{27}FN_3O_6S)_2Ca$ and 1001.14 g/mol

Structural formula:



Physicochemical properties:

Rosuvastatin calcium is a white amorphous powder that is sparingly soluble in water and methanol, and slightly soluble in ethanol.

CLINICAL TRIALS

Comparative Bioavailability Studies

A randomized, single dose, double-blinded, 2-way crossover comparative bioavailability study, conducted under fasting conditions was performed on healthy male volunteers. The rate and extent of absorption of rosuvastatin was measured and compared following a single oral dose (1 x 40 mg tablet) of CRESTOR® (rosuvastatin calcium) and APO-ROSUVASTATIN (rosuvastatin calcium) in 20 volunteers. The results from measured data are summarized in the following table:

Table 4

Summary Table of the Comparative Bioavailability Data
Rosuvastatin
(A single 40 mg dose: 1 x 40 mg)
From Measured Data/Fasting Conditions
Geometric Mean
Arithmetic Mean (CV%)

Parameter	APO-ROSUVASTATIN (Apotex Inc.) (Canada)	CRESTOR®† (AstraZeneca Canada Inc.) (Canada)	Ratio of Geometric Means (%)	90% Confidence Interval (%)
AUCt (ng•h/mL)	141.660 154.344 (42)	146.920 158.408 (39)	96.4	88.7 – 104.9
AUCinf (ng•h/mL)	148.010 161.193 (42)	151.801 163.315 (39)	97.5	90.1 – 105.5
C_{max} (ng/mL)	15.733 17.940 (52)	16.690 18.328 (42)	94.3	83.5 – 106.4
T_{max}§ (h)	4.05 (25)	3.80 (30)		
Thalf§ (h)	19.48 (54)	17.01 (30)		

§ Arithmetic means (CV%) only.
† CRESTOR® is manufactured by AstraZeneca Canada Inc. and was purchased in Canada.

A randomized, single dose, double-blinded, 2-way crossover comparative bioavailability study, conducted under fasting conditions was performed on healthy male volunteers. The rate and extent of absorption of rosuvastatin was measured and compared following a single oral dose (1 x 20 mg tablet) of CRESTOR® (rosuvastatin calcium) and APO-ROSUVASTATIN (rosuvastatin calcium) in 24 volunteers. The results from measured data are summarized in the following table:

Table 5

Summary Table of the Comparative Bioavailability Data Rosuvastatin (A single 20 mg dose: 1 x 20 mg) From Measured Data/Fasting Conditions Geometric Mean Arithmetic Mean (CV %)				
Parameter	APO-ROSUVASTATIN (Apotex Inc.) (Canada)	CRESTOR®† (AstraZeneca Canada Inc.) (Canada)	% Ratio of Geometric Means	90% Confidence Interval
AUCt (ng•h/mL)	58.799 63.969 (41)	55.926 62.332 (49)	105.1	96.4 – 114.6
AUCinf (ng•h/mL)	61.921 66.165 (40)	59.443 65.716 (48)	104.2	95.5 – 113.6
C_{max} (ng/mL)	5.726 6.394 (50)	5.655 6.580 (59)	101.3	89.5 – 114.6
T_{max}§ (h)	4.69 (21)	4.75 (22)		
Thalf§ (h)	16.16 (28)	17.79 (33)		
§ Arithmetic means (CV%) only. † CRESTOR® is manufactured by AstraZeneca Canada Inc. and was purchased in Canada.				

Hypercholesterolemia

Adults

The lowering of total cholesterol, LDL-C, Total-C/HDL-C ratio and ApoB has been shown to reduce the risk of cardiovascular events and mortality.

Rosuvastatin calcium has been shown to significantly improve lipid profiles in patients with a variety of dyslipidemic conditions. Rosuvastatin calcium is highly effective in reducing total-C and LDL-C, TG and ApoB and increasing HDL-C in patients with primary hypercholesterolemia (with and without hypertriglyceridemia), familial and non-familial hypercholesterolemia, mixed hyperlipidemia, and in patients with non-insulin dependent diabetes mellitus (NIDDM). Rosuvastatin calcium also lowers the LDL-C/HDL-C, Total-C/HDL-C, nonHDL-C/HDL-C and the ApoB/ApoA-I ratios.

The following reductions in total cholesterol, LDL-C, TG, Total-C/HDL-C 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 hypercholesterolemia:

Table 6 Dose-Response in Patients with Mild to Moderate Hypercholesterolemia (Mean Percent Change from Baseline)

Rosuvastatin Calcium 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

Dose-Ranging Studies

In clinical trials, rosuvastatin calcium (5 to 40 mg/day) corrected lipid abnormalities in a wide variety of hyperlipidemic and dyslipidemic conditions.

In one multicenter, double-blind, placebo-controlled, dose range study in patients with mild to moderate hypercholesterolemia (Fredrickson Types IIa and IIb), rosuvastatin calcium (given as a single daily dose for 6 weeks) significantly reduced the levels of Total-C (33 to 46%), LDL-C (45 to 63%), Total-C/HDL-C (41 to 51%), ApoB (38 to 54%), TG (10 to 35%) , and increased HDL-C levels (8 to 14%) across the dose range. Approximately 60% of the LDL-C reduction at 6 weeks was attained within 1 week and 90% of the LDL-C reduction was attained within the first 2 weeks after the beginning of therapy.

DETAILED PHARMACOLOGY

Human Pharmacology

Rosuvastatin calcium decreases elevated total cholesterol (Total-C), LDL-C, TG and increases HDL-C in patients with homozygous familial hypercholesterolemia (FH), nonfamilial forms of hypercholesterolemia and mixed dyslipidemia. In these patients rosuvastatin calcium also lowers Apolipoprotein B, nonHDL-C, VLDL-C, VLDL-TG, the LDL-C/HDL-C, Total-C/HDL-C, nonHDL-C/HDL-C, ApoB/ApoA-I ratios and increases ApoA-I.

A therapeutic response to rosuvastatin calcium is evident within 1 week after initiation of therapy and 90% of the maximum response is usually obtained after 2 weeks. The maximum response is generally attained in 4 weeks and has been maintained in clinical trial patients followed-up for up to 1 year.

Animal Pharmacology

Rosuvastatin was shown to be an inhibitor of HMG-CoA reductase in microsomes isolated from rat and human liver. Like other statins, the inhibition was competitive with HMG-CoA and non-competitive with NADPH. Using a cloned fragment of human HMG-CoA reductase, representing the catalytic domain, the estimated inhibition constant (Ki) for rosuvastatin was 0.1 nM. Inhibition of the catalytic domain was also found to be competitive with HMG-CoA and non-competitive with NADPH. Of the metabolites of rosuvastatin that have been detected in humans and animal species, only N-desmethyl rosuvastatin demonstrated notable inhibition of HMG-CoA reductase and was found to be 2 to 7-fold less potent than the parent compound.

Using primary preparations of hepatocytes, rosuvastatin was found to inhibit cholesterol synthesis from acetate, with an IC_{50} about 7-fold lower than the nearest comparator, atorvastatin

and 40-fold lower than pravastatin. Rosuvastatin did not inhibit synthesis of cholesterol from mevalonate (the product of HMG-CoA reductase), indicating no effect on the enzymes of the sterol pathway downstream from HMG-CoA reductase. Compared to a variety of non-hepatic cells including human myoblasts, rosuvastatin was found to be highly selective for action in hepatocytes. Studies of the initial uptake rates of rosuvastatin into rat hepatocytes defined a high affinity component of uptake with a Km of 9 mM. In addition, compared to other statins, rosuvastatin exhibited low rates of metabolism by cytochrome P450-dependent enzymes. The comparatively high potency of effect of rosuvastatin in hepatocytes may result from a combination of high affinity for the enzyme active site, active transport, and low rates of metabolism. The high degree of selectivity for action of the compound in liver cells is consistent with its octanol: water partition and with evidence of active transport into hepatocytes.

Rosuvastatin was shown to inhibit hepatic cholesterol synthesis after oral administration to the rat, with 50 to 80% inhibition of liver HMG-CoA reductase achieved at doses between 1 and 5 mg/kg. The uptake of rosuvastatin from plasma was higher into liver than any other tissue and the peak of inhibition in liver after oral dosing coincided with the peak of plasma rosuvastatin levels. There was evidence of a relatively long duration of action on liver cholesterol synthesis by rosuvastatin compared with other statins.

In the dog, plasma mevalonate levels were rapidly reduced after oral administration of rosuvastatin. The dose required for half maximal reduction of mevalonate measured at 4 hours post-dose, was similar to the dose required to inhibit hepatic cholesterol by 50% in the rat. When 3 mg/kg was administered to dogs once daily for 14 days, rosuvastatin progressively reduced total cholesterol levels by up to 26%. Stable cholesterol-lowering effects were also observed on oral administration of doses of 0.03 to 0.1 mg/kg of rosuvastatin to the dog for three months. In addition, rosuvastatin has been shown to reduce serum cholesterol and lipoprotein levels in the Cynomolgus monkey. Rosuvastatin dose-dependently reduced VLDL and LDL in two strains of hyperlipidemic transgenic mice and reduced VLDL production rates. In the genetically hyperlipidemic WHHL rabbit, rosuvastatin reduced Total and LDL-cholesterol and reduced the extent and degree of atherosclerotic lesions in the aorta.

The effects of rosuvastatin observed *in vitro* and in the animal models are consistent with inhibition of hepatic HMG-CoA reductase as the primary mode of action.

TOXICOLOGY

Acute Toxicity

Rosuvastatin was shown to be of low acute toxicity following administration of single doses to rats and dogs by oral and intravenous routes. There were no mortalities in rats given an oral dose of 1000 mg/kg or 2000 mg/kg, and other than depression of bodyweight at 2000 mg/kg, there were no treatment-related effects at either dose level. Dogs received oral doses of 1000 mg/kg or 2000 mg/kg with vomiting on the day of dosing observed as the major clinical finding in both sexes. Biochemical changes (increased plasma enzymes, decreased lipids) and hematological change (increased white blood cells) were found in dogs given an oral dose of up to and including 2000 mg/kg. Lethality was observed immediately after dosing in 1/1 of rats given an

intravenous dose of 500 mg/kg but two rats given 250 mg/kg intravenously showed slight hypopnea and weakness soon after dosing with no subsequent effects. The results are summarized below:

Table 7 Acute Oral and Intravenous Toxicity Studies with Rosuvastatin

Species	Route	Dose Levels for One or Both Sexes (mg/kg)	Mortalities
Rat	Oral	1000 and 2000	0/1 at 1000 mg/kg; 0/2 at 2000 mg/kg
Rat	Intravenous	250 and 500	1/1 died at 500 mg/kg; 0/2 at 250 mg/kg
Rat	Oral	1000 and 2000	0/12 at 1000 mg/kg; 0/12 at 2000 mg/kg
Dog	Oral	1000 and 2000	0/2 at 1000 mg/kg; 0/2 at 2000 mg/kg

Subacute and Chronic Toxicity

The significant target organs affected by rosuvastatin in multiple dose toxicity studies in rats (14 days to 6 months), mice (2 weeks to 13 weeks), Cynomolgus monkeys (30 days to 6 months), dogs (14 days to 12 months) and rabbits (developmental toxicity study) are summarized in Table 8 below.

Table 8 Rosuvastatin: Target Organs Affected in Animal Studies

Mouse	Rat	Cynomolgus Monkey	Dog	Rabbit
Liver - increased weight and centrilobular hypertrophy	Liver - increased weight, eosinophilia, periportal necrosis and intralobular bile duct hypertrophy, increased liver-related plasma enzymes	Testis - reduced spermatogenic epithelium with vacuolation	Liver — increased liver-related plasma enzymes	Skeletal Muscle - focal degeneration and necrosis of perivascular myocardium and other skeletal muscle tissue
Stomach (non-glandular)** - hyperplasia of squamous epithelium and hyperkeratosis of forestomach mucosa	Stomach (non-glandular)** - hyperplasia of squamous epithelium and hyperkeratosis of forestomach mucosa	Kidney - cortical tubular epithelial cell necrosis with regeneration	Gallbladder -hemorrhage, edema and/or inflammatory cell infiltrate in lamina propria mucosa	
Gall bladder* - hemorrhage, edema and/or inflammatory cell infiltration in lamina propria mucosa			Lens*** - punctate or striate opacities in anterior portion of the lens	
			Brain* - edema, hemorrhage and partial necrosis in choroid plexus	
			Testis - tubular degeneration and atrophy	

* Occurred after administration of high, intolerable doses (250 mg/kg/day [mouse gall bladder], 90 mg kg/day [dog brain])
** Unique anatomical structure not relevant to human
*** Not a consequence of prolonged dosing

Table 9 summarizes the significant adverse changes observed during chronic toxicology studies in the mouse (104 weeks), rat (6 months), dog (12 months), Cynomolgus monkey (6 months) and rabbit (developmental toxicity study).

Table 9: Rosuvastatin: Significant Adverse Changes in Subacute and Chronic Studies

			Margin vs. NOAEL: 40 mg	
Species/Finding	**No-Effect Dose (mg/kg/day)**	**Minimal Toxic Dose (mg/kg/day)**	**C_{max} (adjusted for protein binding (ng/mL)**	**AUC (adjusted for protein binding) (ng·h/mL)**
Mouse				
Liver carcinoma	60	200	19	4.9
Rat				
Forestomach hyperkeratosis	> 20	> 20	12	4
Plasma liver enzymes	> 20	> 20	12	4
Hepatocellular necrosis	2	6	0.44	0.3
Muscle necrosis	80 (2 yr study)	80 (13 wk study)	26	6.5
Uterine polyps	60	80	23	5
Dog				
Plasma liver enzymes	3	6	3.9	4
Hepatocellular atrophy	3	6	3.9	4
Gall bladder edema and hemorrhage	3	6	3.9	4
Ocular opacity	15	30	19	2.4
Testicular tubular degeneration	30	90	33	20
Monkey				
Testicular tubular degeneration	10	30	2.3	4
Renal tubular necrosis	10	30	2.3	4
Rabbit				
Muscle necrosis	1*	3*	0.2**	Not available

* rabbit teratology study ** exposure determined in a separate toxicokinetic study

The toxicology profile of rosuvastatin appears similar to that observed with other statins and is a consequence of its primary pharmacology action (i.e. inhibition of the enzyme, HMG-CoA reductase) which leads to reduced cholesterol synthesis.

Carcinogenicity/Mutagenicity

In a 104-week carcinogenicity study in rats at dose levels of 2, 20, 60 or 80 mg/kg/day, the incidence of uterine polyps was statistically significantly increased only in females at the dose of 80 mg/kg/day. This dose produced a plasma AUC $_{(0\text{-}24)}$ value approximately 8 times higher (after

correction for interspecies differences in protein binding) than the human plasma drug exposure after a 40 mg dose at steady state.

Increased incidences of polyps observed at 2, 20 and 60 mg/kg/day were not statistically different from the control group not exposed to rosuvastatin. The 60 mg/kg/day dose produced a plasma AUC $_{(0\text{-}24)}$ value approximately *5* times higher (after correction for interspecies differences in protein binding) than the mean human exposure after a 40 mg dose at steady state. The occurrence of uterine polyps in old female rats is well-known and is considered benign tumors and lesions termed non-neoplastic in humans.

In a 107-week carcinogenicity study in mice given 10, 60, 200 or 400 mg/kg/day, the 400 mg/kg/day dose was poorly tolerated, resulting in early termination of this dose group. An increased incidence of hepatocellular carcinomas was observed at 200 mg/kg/day and an increase in hepatocellular adenomas was seen at 60 and 200 mg/kg/day. The dose of 200 mg/kg/day produced a plasma AUC $_{(0\text{-}24)}$ value approximately 37 times higher (after correction for interspecies differences in protein binding) than the mean human plasma drug exposure after a 40 mg dose at steady state. An increased incidence of hepatocellular tumors was not seen at 10 mg/kg/day. The 60 mg/kg/day dose produced a plasma AUC$_{(0\text{-}24)}$ value approximately 4.9 times higher (after correction for interspecies differences in protein binding) than the mean human plasma drug exposure after a 40 mg dose at steady state. These hepatocellular effects are known to occur in rodents treated with statins without evidence of similar effects in humans.

In vitro, rosuvastatin was not mutagenic or clastogenic with or without metabolic activation in the Ames test with *Salmonella typhimurium* and *Escherichia coli*, L-5178 y ± mouse lymphomas, and the chromosomal aberration assay in Chinese hamster lung cells. Rosuvastatin was negative in the *in vivo* mouse micronucleus test.

Teratology and Reproductive Studies

The reproductive toxicity of rosuvastatin has been evaluated in fertility and pre- and post-natal developmental studies, at doses up to 50 mg/kg/day. Slight reductions in maternal body weight gain and food consumption were observed at 50 mg/kg/day. Rosuvastatin had no adverse effects on mating, fertility in both sexes, implantation and maintenance of pregnancy, pup morphology or survival at 50 mg/kg/day in the fertility study. In a pre- and post-natal sighting study in rats given ≥ 75 mg/kg/day there was reduced pup survival at birth at 125 and 150 mg/kg/day and during early lactation at 75 and 100 mg/kg/day. In the main pre- and post-natal developmental study, rosuvastatin showed no adverse effects on the duration of pregnancy, delivery and lactation in the dams in either generation at the high dose of 50 mg/kg/day. In the absence of plasma AUC exposure data in pregnant rats, comparisons with human data have been made on a received dose basis. The dose of 50 mg/kg/day equates to 90 times the human dose of 40 mg given to a 70 kg human.

The potential of rosuvastatin to cause developmental toxicity has been examined in the pregnant rat at doses up to 100 mg/kg/day and in the pregnant rabbit at doses up to 3 mg/kg/day. Rosuvastatin was shown to be neither embryo-fetolethal nor teratogenic in rats. At a maternally toxic dose of 3 mg/kg/day in rabbits, fetal examination showed no evidence of fetolethality or

teratogenicity.

Overall, rosuvastatin has shown no reproductive or developmental toxicity.