PRODUCT MONOGRAPH

[Pr] MYLAN-ROSUVASTATIN

Rosuvastatin Calcium Tablets

5 mg, 10 mg, 20 mg and 40 mg

LIPID METABOLISM REGULATOR

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Rosuvastatin Calcium Tablets

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	Cellulose microcrystalline, crospovidone, iron oxide red, lactose monohydrate, magnesium oxide, magnesium stearate, silica colloidal anhydrous. Coating: FD&C Blue #2/Indigo Carmine Aluminium Lake, FD&C Red #40/Allura Red AC Aluminium Lake, FD&C Yellow #5/Tartrazine Aluminium Lake (5 mg tablet only), FD&C Yellow #6/Sunset Yellow FCF Aluminium Lake (10 mg, 20 mg, and 40 mg tablets only), HPMC 2910/Hypromellose 15cP, lactose monohydrate, titanium dioxide, triacetin.

INDICATIONS AND CLINICAL USE

Hypercholesterolemia

Adults

MYLAN-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:

- Severe non-familial hypercholesterolemia
- Combined (mixed) dyslipidemia (Type IIb)

- Homozygous familial hypercholesterolemia where MYLAN-ROSUVASTATIN is used either alone or as an adjunct to diet and other lipid lowering treatments such as apheresis.

Prevention of Major Cardiovascular Events

In adult patients without documented history of cardiovascular or cerebrovascular events, but with at least two conventional risk factors for cardiovascular disease (see CLINICAL TRIALS), MYLAN-ROSUVASTATIN is indicated to:

- Reduce the risk of nonfatal myocardial infarction
- Reduce the risk of nonfatal stroke
- Reduce the risk of coronary artery revascularization

CONTRAINDICATIONS

MYLAN-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). MYLAN-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 MYLAN-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).

MYLAN-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 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 DRUG INTERACTIONS and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

WARNINGS AND PRECAUTIONS

General

Before instituting therapy with MYLAN-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 rosuvastatin calcium 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

MYLAN-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 MYLAN-ROSUVASTATIN or if the patient is titrated to the dose of 40 mg. MYLAN-ROSUVASTATIN should be discontinued or the dose reduced if the level of transaminases is greater than 3 times the upper limit of normal.

MYLAN-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 MYLAN-ROSUVASTATIN, promptly interrupt therapy. If an alternate etiology is not found, do not restart MYLAN-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. Rosuvastatin calcium therapy should be discontinued if markedly elevated CK levels (> 10 x ULN) are measured or myopathy is diagnosed or suspected.

- There have been very rare reports of an 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

MYLAN-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 DRUG INTERACTIONS 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.

MYLAN-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/1.73m^2) had a 3-fold increase in plasma concentration of rosuvastatin compared to healthy volunteers and, therefore, MYLAN-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:

MYLAN-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 MYLAN-ROSUVASTATIN should not breast-feed (see CONTRAINDICATIONS).

Pediatrics (≤ 18 years of age):

Mylan-Rosuvastatin is not indicated for children less than 18 years old. Adolescent females should be counselled on appropriate contraceptive methods while on rosuvastatin calcium therapy (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women).

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		
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

Body System/Adverse Event	Placebo (%) (N=367)	Total rosuvastatin (%) (N=768)
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 (see Part II: CLINICAL TRIALS) 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
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).

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 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: Rosuvastatin calcium 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.

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	Rosuvastatin calcium 10 and 20 mg were administered to cardiac	The concomitant use of rosuvastatin calcium and cyclosporine is

Proper Name	Effect	Clinical Comment
Cyclosporine)	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.	contraindicated (see CONTRAINDICATIONS).
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 $AUC_{(0-24)}$. 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. 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 $AUC_{(0-24)}$. Darunavir 600 mg /ritonavir 100 mg (BID, 7 days), rosuvastatin	For co-administration with atazanavir/ritonavir, or simeprevir, the dose of rosuvastatin calcium should not exceed 10 mg daily. For co-administration with lopinavir/ritonavir, darunavir/ritonavir or tipranavir/ritonavir, the dose of rosuvastatin calcium should not exceed 20 mg daily.

Proper Name	Effect	Clinical Comment
	calcium 10 mg (OD, 7 days); approximately a 1.5-fold increase in rosuvastatin mean $AUC_{(0-24)}$. Tipranavir 500 mg /ritonavir 200 mg (BID, 11 days), rosuvastatin calcium 10 mg (single dose); approximately a 1.4-fold increase in rosuvastatin mean $AUC_{(0-24)}$. Fosamprenavir 700 mg /ritonavir 100 mg (OD, 8 days), rosuvastatin calcium 10 mg (single dose); no significant change in rosuvastatin mean $AUC_{(0-24)}$.	
Gemfibrozil	Coadministration of a single rosuvastatin dose (10 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 rosuvastatin calcium and gemfibrozil should be avoided. If used together, the dose of rosuvastatin calcium should not exceed 20 mg once 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 rosuvastatin calcium should not exceed 20 mg daily when used concomitantly with clopidogrel.
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 rosuvastatin calcium 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	The dose of rosuvastatin calcium should not exceed 20 mg daily when used concomitantly with dronedarone.

Proper Name	Effect	Clinical Comment
	rosuvastatin.	
Itraconazole	Coadministration of rosuvastatin calcium 10 mg (single dose) with itraconzaole 200 mg (OD, 5 days) to healthy volunteers resulted in a 1.4-fold increase in the mean AUC of rosuvastatin.	The dose of rosuvastatin calcium should not exceed 20 mg daily when used concomitantly with itraconazole.
Coumarin Anticoagulants	As with other HMG-CoA reductase inhibitors, coadministration of rosuvastatin calcium 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 relevant in patients using this type of antacid infrequently. A frequent antacid user should be instructed to take rosuvastatin calcium at a time of day when they are less likely to

Proper Name	Effect	Clinical Comment
		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 rosuvastatin calcium with fusidic acid should be avoided. Temporary suspension of 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 μg] and norgestrel [180 μg on days 1 to 7, 215 μg on days 8 to 15, and 250 μg 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 MYLAN-ROSUVASTATIN with other medicines known to increase exposure to rosuvastatin, doses of MYLAN-ROSUVASTATIN should be adjusted. Start with a 5 mg once daily dose of MYLAN-ROSUVASTATIN if the expected increase in exposure (AUC) is approximately 2 fold or higher. The maximum daily dose of MYLAN-ROSUVASTATIN should be adjusted so that the expected rosuvastatin exposure would not likely exceed that of a 40 mg daily dose of MYLAN-ROSUVASTATIN taken without interacting medicines (see CONTRAINDICATIONS and DRUG INTERACTIONS, Drug-Drug Interactions (Table 3)).

Drug-Food Interactions

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

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

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

Recommended Dose and Dosage Adjustment

Adults

Hypercholesterolemia

The dose range of MYLAN-ROSUVASTATIN is 5 to 40 mg orally once a day. The recommended starting dose of MYLAN-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 2-4 weeks and is maintained during chronic therapy.

Initiation of therapy with MYLAN-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 MYLAN-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 MYLAN-ROSUVASTATIN 40 mg dose.

The dosage of MYLAN-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.

Prevention of Major Cardiovascular Events

A dose of 20 mg once daily has been found to reduce the risk of major cardiovascular events (see CLINICAL TRIALS).

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 MYLAN-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/1.73 m^2) the starting dose of MYLAN-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 MYLAN-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 MYLAN-ROSUVASTATIN 20 mg once daily (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Special Populations, Race).

Use in Children:

Mylan-Rosuvastatin is not indicated for children less than 18 years old.

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 MYLAN-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 MYLAN-ROSUVASTATIN is administered concomitantly with certain medicines that may increase the plasma concentration of rosuvastatin due to interactions with these transporter proteins (e.g. cyclosporine and certain protease inhibitors including combinations of ritonavir with atazanavir, darunavir, lopinavir, and/or tipranavir, see DRUG INTERACTIONS). Whenever possible, alternative medications should be considered, and if necessary, consider temporarily discontinuing MYLAN-ROSUVASTATIN therapy. In situations where coadministration of these medicines with MYLAN-ROSUVASTATIN is unavoidable, the benefit and the risk of concurrent treatment and MYLAN-ROSUVASTATIN dosing adjustments should be carefully considered (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre Immediately.

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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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:

Rosuvastatin calcium 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. Rosuvastatin calcium 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:

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 between 15°C and 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms and Packaging

MYLAN-ROSUVASTATIN (rosuvastatin calcium) is available in tablets of 5 mg, 10 mg, 20 mg and 40 mg.

5 mg - A yellow, film coated, round, biconvex tablet debossed with "M" on one side and "RC" on the other side. Available in blisters of 2 x 15 tablets and high-density polyethylene (HDPE) bottles of 100 and 500 tablets.

10 mg - A pink, film coated, round, biconvex tablet debossed with "M" on one side and "RC1" on the other side. Available in blisters of 2 x 15 tablets and HDPE bottles of 100 and 500 tablets.

20 mg - A pink, film coated, round, biconvex tablet debossed with "M" on one side and "RC2" on the other side. Available in blisters of 2 x 15 tablets and HDPE bottles of 100 and 500 tablets.

40 mg - A pink, film coated, oval, biconvex tablet debossed with "M" on one side and "RC4" on the other side. Available in blisters of 2 x 15 tablets and HDPE bottles of 100 tablets.

Composition

Each tablet contains 5 mg, 10 mg, 20 mg, or 40 mg of rosuvastatin as rosuvastatin calcium and the following non-medicinal ingredients: cellulose microcrystalline, crospovidone, iron oxide red, lactose monohydrate, magnesium oxide, magnesium stearate and silica colloidal anhydrous. The coating contains: FD&C Blue #2/Indigo Carmine Aluminium Lake, FD&C Red #40/Allura Red AC Aluminium Lake, FD&C Yellow #5/Tartrazine Aluminium Lake (5 mg tablet only), FD&C Yellow #6/Sunset Yellow FCF Aluminium Lake (10 mg, 20 mg, and 40 mg tablets only), HPMC 2910/Hypromellose 15cP, lactose monohydrate, titanium dioxide and triacetin.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

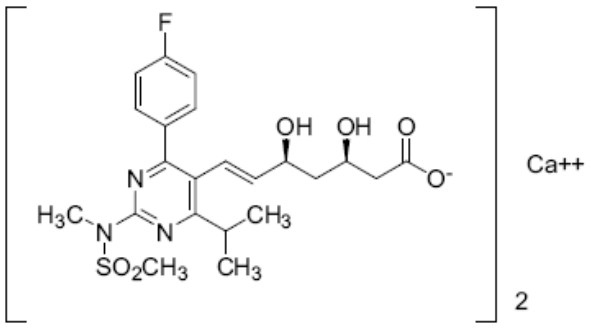
Drug Substance

Proper 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: $C_{44}H_{54}F_2N_6O_{12}S_2Ca$ 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 blinded, balanced, randomized, two-treatment, two-sequence, two-period, single-dose, cross-over, bioequivalence study comparing Mylan-Rosuvastatin (rosuvastatin calcium) 40 mg tablets (Mylan Pharmaceuticals ULC) with Crestor® (rosuvastatin calcium) 40 mg tablets (Astra Zeneca Canada Inc.) in 26 healthy, adult, male South Asian subjects, under fasting condition was conducted.

A summary of the results is presented in the following table.

Rosuvastatin (1 × 40 mg) From measured data **Geometric Mean Arithmetic Mean (CV %)**				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng•h/mL)	372.3 406.7 (44.3)	377.3 414.3 (48.8)	98.68	90.87-107.15
AUC_I (ng•h/mL)	385.9 419.9 (43.2)	390.1 427.0 (48.0)	98.92	91.27-107.22
C_{max} (ng/mL)	46.46 53.30 (59.30)	46.35 52.05 (54.70)	100.24	88.70-113.28
T_{max}§ (h)	4.5 (0.5-6.0)	4.5 (0.5-6.0)		
$T_{½}$€ (h)	11.12 (37.01)	10.52 (41.28)		

*Pr Mylan-Rosuvastatin 40 mg tablets (Mylan Pharmaceuticals ULC).
† Pr CRESTOR® 40 mg tablets (AstraZeneca Canada Inc.) were purchased in Canada.
§ Expressed as the median (range) only.
€ Expressed as the arithmetic mean (CV%) only.

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 4 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 (33-46%), LDL-C (45- 63%), Total-C/HDL-C (41-51%), ApoB (38-54%), TG (10-35%) and increased HDL-C levels (8-14%) 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.

Prevention of Major Cardiovascular Events

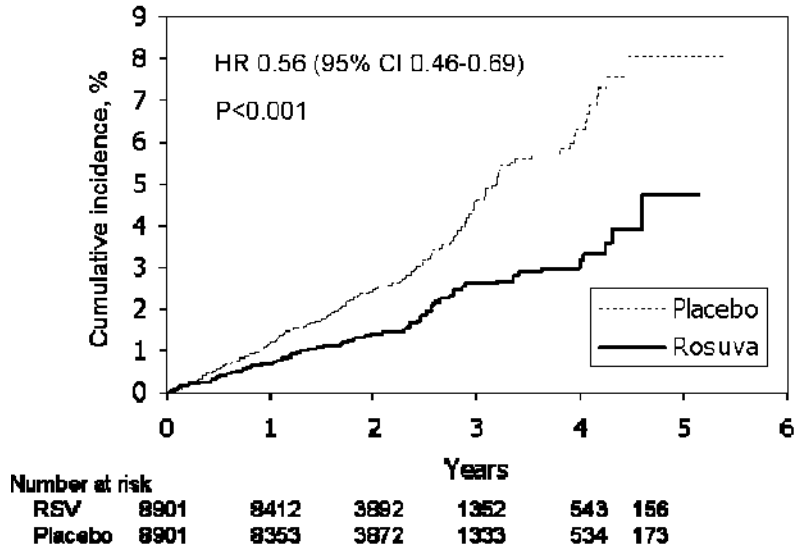
In the JUPITER study (**J**ustification for the **U**se of Statins in **P**rimary Prevention: An **I**ntervention **T**rial **E**valuating **R**osuvastatin) 89,846 people with no pre-existing cardiovascular disease were screened and 17,802 (19.8%) were double-blindly randomized to rosuvastatin calcium 20 mg once daily (n=8901) or placebo (n=8901). Patients were followed for a median duration of 1.9 years. The main reasons for exclusion of patients were due to LDL-C ≥ 3.3 mmol/L (52%) or high sensitivity C-reactive protein (hsCRP) < 2 mg/L (36%). The study population consisted of 11,001 men (≥ 50 years) and 6801 women (≥ 60 years) without history of cardiovascular disease, LDL-C levels < 3.3 mmol/L and hsCRP levels ≥ 2 mg/L. Approximately 50% of the patients had an intermediate (10-20%) Framingham risk category and less than 10% were in the Framingham high (> 20%) risk category. It also included a high percentage of patients with additional risk factors such as

hypertension (58%), low HDLC levels (23%), cigarette smoking (16%), a family history of premature coronary heart disease (CHD) (12%) or prediabetes (31%). Most had two (49%) or three (22%) coronary risk factors at baseline. The JUPITER study was stopped early by the Data Safety Monitoring Board due to meeting predefined stopping rules for efficacy in rosuvastatin-treated subjects.

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

Treatment with rosuvastatin calcium significantly reduced the risk of cardiovascular events ($p<0.001$). When the study was prematurely terminated (median follow-up of 1.9 years and maximal follow-up of 5 years), 142 events in the rosuvastatin calcium group and 252 events in the placebo group had occurred for a relative risk reduction of 44% and absolute risk reduction of 1.23% (see Figure 1). The benefit was apparent within the first 6 months of treatment ($p=0.029$).

Figure 1 Time to First Occurrence of Major Cardiovascular Events



The results of the primary composite endpoint and the individual components are presented in Table 6. Rosuvastatin calcium significantly reduced the risk of nonfatal myocardial infarction ($p < 0.0001$), nonfatal stroke ($p=0.004$) and arterial revascularization procedures ($p=0.034$). There were no statistically significant treatment differences between the rosuvastatin calcium and placebo groups for death due to cardiovascular causes or hospitalizations for unstable angina.

Table 5 Number of First Events by Treatment Group for the Composite Primary Endpoint (ITT population)

	Rosuvastatin calcium N= 8901 n (%)	Placebo N= 8901 n (%)	Relative risk reduction[£] (95% CI)	Absolute Risk Reduction (%)	1.9 year NNT
PRIMARY (composite) ENDPOINT	142 (1.6)	252 (2.83)	44% (31, 54)	1.23	81
COMPONENTS OF PRIMARY ENDPOINT					
Cardiovascular death[∞]	29 (0.33)	37 (0.42)	22% (-27, 52)	0.09	1112
Nonfatal stroke	30 (0.34)	57 (0.64)	48% (18, 66)	0.30	329
Nonfatal MI	21 (0.24)	61 (0.69)	66% (44, 79)	0.45	222
Unstable angina	15 (0.17)	27 (0.30)	45% (-4, 71)	0.13	741
Arterial revascularization	47 (0.53)	70 (0.79)	33% (3, 54)	0.26	387

[∞] Cardiovascular death included fatal MI, fatal stroke, sudden death, and other adjudicated causes of CV death,

[£] Negative numbers imply a risk increase,

CI Confidence interval, ITT Intent-to-treat, MI myocardial infarction, NNT number needed to treat.

Rosuvastatin calcium significantly reduced the risk of the combined secondary endpoint of fatal and nonfatal myocardial infarction (HR 0.46, 95% CI 0.30-0.70, p<0.0002) (6 fatal events and 62 nonfatal events in placebo-treated subjects versus 9 fatal events and 22 nonfatal events in rosuvastatin calcium-treated subjects) and the risk of the combined secondary endpoint of fatal and nonfatal stroke (HR 0.52, 95% CI 0.34-0.79, p=0.002) (6 fatal events and 58 nonfatal events in placebo-treated subjects versus 3 fatal events and 30 nonfatal events in rosuvastatin calcium-treated subjects).

Risk reduction observed was as a rule similar across multiple predefined population subsets based on age, gender, race, smoking status, family history of premature CHD, body mass index, LDL-C, HDL-C, serum triglyceride, fasting glucose level (< 5.6 mM and ≥ 5.6 mM), metabolic syndrome, or hsCRP levels (above and below the median 4.2 mg/L) at the time of entry into the study.

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, VLDLC, 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 K_m 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 6 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 7 below.

Table 7 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 8 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 8 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 $AUC_{(0-24)}$ 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 $AUC_{(0-24)}$ 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 $AUC_{(0-24)}$ 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 $AUC_{(0-24)}$ 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 postnatal 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.

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PART III: CONSUMER INFORMATION

[Pr] MYLAN-ROSUVASTATIN

Rosuvastatin Calcium Tablets

This leaflet is part of a "Product Monograph" published when MYLAN-ROSUVASTATIN was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about MYLAN-ROSUVASTATIN. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What MYLAN-ROSUVASTATIN is used for:
Your doctor has prescribed these pills to help lower your cholesterol or other fats in the blood (such as triglycerides) and lower the risk of heart attacks and strokes.

What MYLAN-ROSUVASTATIN does:
MYLAN-ROSUVASTATIN is the brand name for rosuvastatin that belongs to the class of medications known as "statins", more specifically called HMG-CoA reductase inhibitors. HMG-CoA reductase is an enzyme involved in regulating cholesterol levels in your body. Statins are used along with changes to diet and exercise to help control the amount of cholesterol produced by the body.

MYLAN-ROSUVASTATIN can help your body:
- decrease LDL (bad) cholesterol and triglyceride levels.
- increase HDL (good) cholesterol levels.
- decrease the Total Cholesterol/HDL-Cholesterol Ratio (TC: HDL-C Ratio). The ratio represents the balance between good and bad cholesterol.

What is cholesterol?
Cholesterol is one of several fatty substances in the blood that the body needs to function. And it is important to our health. Our bodies use cholesterol in a number of ways; for example, to produce bile acids that help you digest fat.

High cholesterol levels may not make you feel or look sick. However, too much cholesterol in your blood can be unhealthy; it builds up on the artery walls and can lead to the signs and symptoms of cardiovascular disease (heart disease).

There are two very different types of cholesterol.

LDL cholesterol
If levels of LDL cholesterol are too high, they can cause the gradual build-up of cholesterol called plaque on the walls of the blood vessels. Over time, this plaque can build up so much that it narrows the arteries. Narrow arteries can slow or block blood flow to vital organs like the heart and brain. Blocked blood flow can result in a heart attack or stroke.

HDL cholesterol
HDL carries the LDL cholesterol away from the blood vessel walls to the liver, where it can be removed from the body. A higher level of HDL cholesterol is good.

Important cholesterol targets
There are a few important measures that relate to your cholesterol. In addition to your HDL and LDL cholesterol, your doctor may also track your TC:HDL-C Ratio.

Lowering LDL cholesterol and Ratio
There are many things you can do, depending on your health and lifestyle, to help lower LDL cholesterol, increase HDL cholesterol and lower your TC: HDL-C Ratio. Your doctor may recommend:

- A change in your diet to control your weight and/or lower your cholesterol.
- Exercise that is right for you.
- Quitting smoking and avoiding smoky places.
- Giving up alcohol or drinking less.

Follow your doctor's instructions carefully.

When MYLAN-ROSUVASTATIN should not be used:
Do not take MYLAN-ROSUVASTATIN if you:
- Currently have liver disease.
- Are pregnant or think you might be pregnant. If you become pregnant while taking MYLAN-ROSUVASTATIN, discontinue use immediately and discuss with your doctor, as MYLAN-ROSUVASTATIN should not be used by pregnant women.
- Are breast-feeding.
- Have ever had an allergic reaction to the active ingredient or any of the other ingredients in

MYLAN-ROSUVASTATIN (**see What the nonmedicinal ingredients are:**).
- Are taking a drug called cyclosporine (used, for example, after organ transplant).

What the medicinal ingredient is:
Rosuvastatin calcium.

What the nonmedicinal ingredients are:
Cellulose microcrystalline, crospovidone, iron oxide red, lactose monohydrate, magnesium oxide, magnesium stearate, silica colloidal anhydrous. Coating: FD&C Blue #2/Indigo Carmine Aluminium Lake, FD&C Red #40/Allura Red AC Aluminium Lake, FD&C Yellow #5/Tartrazine Aluminium Lake (5 mg tablet only), FD&C Yellow #6/Sunset Yellow FCF Aluminium Lake (10 mg, 20 mg, and 40 mg tablets only), HPMC 2910/Hypromellose 15cP, lactose monohydrate, titanium dioxide, triacetin.

MYLAN-ROSUVASTATIN contains lactose and colouring agents but does not contain gluten.

What dosage form it comes in:
MYLAN-ROSUVASTATIN film-coated tablets are available in 4 tablet strengths: 5 mg, 10 mg, 20 mg and 40 mg.

WARNINGS AND PRECAUTIONS

Pregnancy
MYLAN-ROSUVASTATIN should not be used by pregnant women. Cholesterol compounds are essential elements for the development of a fetus. Cholesterol-lowering drugs can harm the fetus. If you become pregnant, discontinue use immediately and tell your doctor.

If you are of childbearing age, discuss with your doctor the potential risks and the importance of birth control methods.

Before taking your MYLAN-ROSUVASTATIN tablets, tell your doctor or pharmacist if you:
- Have thyroid problems.
- Regularly drink *three or more* alcoholic drinks daily.
- Have a family history of muscular disorders.
- Had any past problems with your muscles (pain, tenderness), after using an HMG-CoA reductase inhibitor (statin) such as atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin or simvastatin, or have developed an allergy or intolerance to them.
- Have kidney or liver problems.
- Have diabetes.
- Have undergone surgery or other tissue injury.
- Do excessive physical exercise.

Slightly increased blood sugar can occur when you take MYLAN-ROSUVASTATIN. You are likely to be at risk of developing diabetes if you have high levels of sugar and fats in your blood, are overweight and have high blood pressure. Discuss with your doctor your risk of developing diabetes.

INTERACTIONS WITH THIS MEDICATION

Sometimes drugs can interact with other drugs, so tell your doctor or pharmacist if you are taking any other medications, including prescription, non-prescription and natural health products. In particular, tell your doctor if you are taking any of the following:
- Any other cholesterol-lowering medications such as fibrates (gemfibrozil, fenofibrate), niacin or ezetimibe.
- Warfarin, clopidogrel (or any other drug for thinning the blood).
- Antiviral medications such as ritonavir combined with another protease inhibitor or simeprevir (used to fight infections, including the HIV infection or Hepatitis C infection).
- Antacids (frequent use) and MYLAN-ROSUVASTATIN should be taken 2 hours apart.
- Cyclosporine (used after organ transplant).
- Fusidic acid (an antibiotic agent). Your doctor may temporarily stop your treatment of MYLAN-ROSUVASTATIN until the treatment with fusidic acid is complete.

PROPER USE OF THIS MEDICATION

Your doctor prescribed this medicine only for you. Do not give your medicine to anyone else because it may harm them, even if their symptoms are the same as yours.

Always follow your doctor's instructions carefully and keep taking your medicine even if you feel well.

- Swallow each tablet whole with a drink of water. Take MYLAN-ROSUVASTATIN as a single dose.
- Remember to take MYLAN-ROSUVASTATIN at the same time every day. It does not matter if you take MYLAN-

ROSUVASTATIN with or without food, or in the morning or evening.
- Do not change the dose or stop taking the medicine without first talking to your doctor.
- If you get sick, have an operation, or need medical treatment while you are taking MYLAN-ROSUVASTATIN, let the doctor or pharmacist know that you are taking MYLAN-ROSUVASTATIN.
- If you have to see a different doctor, for any reason, be sure to tell him/her of any medicines you might be taking, including MYLAN-ROSUVASTATIN.

To help you keep track of your doses, MYLAN-ROSUVASTATIN comes in a blister pack with days of the week printed on the back of the blister. Start with the tablet that matches the day of the week and continue taking them in order until they are all finished.

There are 14 days of labeled tablets in each blister, with one extra to make 15. All 15 tablets, including the one labeled “Take this tablet last”, are exactly the same. Once you have finished the 14 labeled tablets, take the one marked "Take this tablet last" before starting your next blister pack.

Remember to get a new prescription from your doctor or a refill from your pharmacy a few days before all your tablets are taken.

Usual dose:
Adults
Treatment with MYLAN-ROSUVASTATIN is usually started with one 10 mg tablet taken once daily. Some people may be asked to start treatment with one 5 mg tablet taken once a day while others may be asked to start with one 20 mg tablet taken once a day.

After checking the amount of lipids in your blood, your doctor may decide to adjust your dose until you are taking the amount of MYLAN-ROSUVASTATIN that is right for you. The maximum daily dose is 40 mg.

Overdose:

There is no specific treatment in the event of an overdose.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed dose:
Do not take a double dose. If you miss taking a tablet, take it as soon as you can. But if it is almost time for your next dose, skip the missed dose and just take the next dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Most people do not have side effects when taking rosuvastatin calcium. However, all medicines can cause unwanted side effects. These effects are usually mild and disappear after a short time.

Check with your doctor or pharmacist promptly if any of the following persist or become troublesome:
- Stomach pain
- Headache
- Constipation
- Dizziness
- Feeling sick

Less commonly, some people may have other side effects such as a skin rash, itching and hives.

MYLAN-ROSUVATSTIN can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

Possible side effects reported with some statins: breathing problems including persistent cough and/or shortness of breath or fever; confusion, poor memory, mood problems including depression; problems sleeping including insomnia and nightmares; erectile dysfunction; numbness, tingling, weakness or pain, usually in your hands or feet, but this may also occur in other areas of your body (peripheral neuropathy).

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / Effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Rare	Muscle pain that you cannot explain		√	
	Muscle tenderness or weakness, or		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / Effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
	joint pain			
	Breast enlargement in women and men (gynecomastia)		√	
	Generalized weakness, especially if you do not feel well		√	
	Jaundice or hepatitis symptoms like brownish or discoloured urine		√	
	Difficulty in breathing or swallowing			√
	Allergic reaction (symptoms include swelling in the mouth, tongue, face and throat, severe itching, rash, raised lumps (hives), blistering of the skin and mucous membranes of the lips, eyes, mouth, nasal passages or genitals)			√
	Liver damage: yellowing of the skin or eyes, flu-like symptoms			√
Very rare	Inflamed pancreas (pancreatitis) symptoms, such as severe stomach pain		√	
	Memory loss		√	
Unknown	Increased blood sugar: frequent urination, thirst and hunger	√		
	Decrease of platelets in the blood (characterized by easy or excessive bleeding such as bruising easily, nosebleed and bleeding gums)			

This is not a complete list of side effects. For any unexpected effects while taking MYLAN-ROSUVASTATIN, contact your doctor or pharmacist.

HOW TO STORE IT

- KEEP YOUR TABLETS IN A SAFE PLACE where children cannot see or reach them. Your tablets could harm them.
- Keep your medicine at room temperature (15°C-30°C), away from warm or damp places like bathrooms or kitchens.
- Keep your tablets in the package they came in.
- If your doctor decides to stop your treatment, return your tablets to your pharmacist for disposal.
- Do not take your tablets after the expiry date on the package.

Reporting Side Effects

- You can report any suspected side effects associated with the use of health products to Health Canada by: Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about Mylan-Rosuvastatin:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); or by calling 1-800-575-1379

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