PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrSANDOZ ROSUVASTATIN

Rosuvastatin Calcium Tablets

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

Manufacturer's Standard

Lipid Metabolism Regulator

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, Musculoskeletal	02/2023
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4.2 Recommended Dose and Dosage Adjustment	12/2023

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Sandoz Rosuvastatin (rosuvastatin calcium) is indicated in adults 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 heterozygous familial hypercholesterolemia and severe non-familial hypercholesterolemia)
- Combined (mixed) dyslipidemia (Type IIb)
- Homozygous familial hypercholesterolemia where Sandoz Rosuvastatin is used either alone or as an adjunct to diet and other lipid lowering treatments such as apheresis.

In adult patients without documented history of cardiovascular or cerebrovascular events, but with at least two conventional risk factors for cardiovascular disease (see 14 CLINICAL TRIALS), Sandoz Rosuvastatin is indicated to:

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

1.1 Pediatrics

Pediatrics (10 to <18 years): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Sandoz Rosuvastatin in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use as an adjunct to diet to reduce elevated total cholesterol (Total-C), LDL-C and ApoB in boys and girls who are at least one year post-menarche with heterozygous familial hypercholesterolemia (see 14 CLINICAL TRIALS), when response to diet alone has been inadequate.

Pediatrics (<10 years of age): No data are available to Health Canada for pediatric patients under the age of 10; therefore, Health Canada has not authorized an indication for pediatric use in this age range.

1.2 Geriatrics

Geriatrics: Evidence from clinical studies and experience suggests that use in the geriatric population is not associated with differences in effectiveness. However, elderly patients may be more susceptible to myopathy (see 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

Sandoz Rosuvastatin (rosuvastatin calcium) is contraindicated in:

- patients who are hypersensitive to any component of this medication (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).
- patients with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal (see 7 WARNINGS AND PRECAUTIONS).
- pregnant and breast-feeding women.
- patients using concomitant cyclosporine (see 9 DRUG INTERACTIONS).
- patients using concomitant sofosbuvir/velpatasvir/voxilaprevir (see 9 DRUG INTERACTIONS).

Sandoz Rosuvastatin **40 mg** is contraindicated in:

- Asian patients
- Patients with pre-disposing factors for myopathy/rhabdomyolysis (see 7 WARNINGS AND PRECAUTIONS, Musculoskeletal).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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 Sandoz Rosuvastatin (rosuvastatin calcium), and should continue on this diet during treatment with Sandoz Rosuvastatin. If appropriate, a program of weight control and physical exercise should be implemented.
Prior to initiating therapy with Sandoz Rosuvastatin, secondary causes for elevations in plasma lipid levels should be excluded. A lipid profile should also be performed.

4.2 Recommended Dose and Dosage Adjustment

Hypercholesterolemia
The dose range of Sandoz Rosuvastatin in adults is 5 to 40 mg orally once a day. The recommended starting dose of Sandoz Rosuvastatin in most adult patients is 10 mg orally once daily. The majority of adult 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 Sandoz Rosuvastatin 5 mg once daily may be considered for adult patients requiring less aggressive LDL-C reductions or who have predisposing factors for myopathy (see 7 WARNINGS AND PRECAUTIONS, Musculoskeletal).

Adult patients who are switched to Sandoz 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 adult 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 adult patients with severe hypercholesterolemia who do not achieve the desired effect on 20 mg and have no predisposing factors for myopathy/rhabdomyolysis (see 2 CONTRAINDICATIONS). Consultation with a specialist is recommended when initiating Sandoz Rosuvastatin 40 mg dose.

The dosage of Sandoz 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 14 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 Sandoz Rosuvastatin should not exceed 20 mg once daily (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, 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 Sandoz Rosuvastatin should be 5 mg and not exceed 10 mg once daily (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Renal Impairment).

- **Ethnic Origin:** The initial dose of Sandoz 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 Sandoz Rosuvastatin 20 mg once daily (see 2 CONTRAINDICATIONS and 7.1 Special Populations, Ethnic Origin).

- **Pediatrics (10 – <18 years of age):** In pediatric patients with heterozygous familial hypercholesterolemia the recommended starting dose of Sandoz Rosuvastatin is 5 mg taken orally once daily. The Sandoz Rosuvastatin dose should be individualized according to baseline LDL-C levels and the recommended goal of therapy. The maximum daily dose in this patient population is 10 mg.

The safety and efficacy of rosuvastatin calcium doses greater than 20 mg have not been studied in this population.

Treatment experience with rosuvastatin calcium in pediatric patients (aged 8 years and above) with homozygous familial hypercholesterolemia is limited to 8 patients. Use in this patient population should be supervised by specialists (see 7.1.3 Pediatrics).

- **Geriatrics (> 65 years of age):** No dose adjustment is necessary in the elderly (see 7.1.4 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 Sandoz Rosuvastatin is recommended (see 7 WARNINGS AND PRECAUTIONS, 9 DRUG INTERACTIONS, and 10.3 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 rosuvastatin calcium is administered concomitantly with certain medicines that may increase the plasma concentration of rosuvastatin due to interactions with these transporter proteins (see Table 4). Whenever possible, alternative medications should be considered, and if necessary, consider temporarily discontinuing Sandoz Rosuvastatin therapy. In situations where coadministration of these medicines with Sandoz Rosuvastatin is unavoidable, the benefit and the risk of concurrent treatment and Sandoz Rosuvastatin dosing adjustments should be carefully considered (see 7 WARNINGS AND PRECAUTIONS and 10.3 Pharmacokinetics, Special Populations and Conditions).

- **Drug discontinuation**
  If the patient becomes pregnant while taking Sandoz Rosuvastatin, the drug should be discontinued immediately and the patient apprised of the potential harm to the fetus.

  Sandoz 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).

  Sandoz Rosuvastatin should be discontinued or the dose reduced if the level of transaminases is greater than 3 times the upper limit of normal.

  Sandoz Rosuvastatin therapy should be discontinued if markedly elevated CK levels (> 10 x ULN) are measured or myopathy is diagnosed or suspected.

  Treatment should be discontinued if hypersensitivity is suspected.

If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Sandoz Rosuvastatin therapy should be discontinued if induction or aggravation of myasthenia gravis is suspected (see 7 WARNINGS AND PRECAUTIONS).

4.4 Administration

Sandoz Rosuvastatin may be taken in the morning or evening, with or without food.

4.5 Missed Dose

A missed dose should be taken as soon as possible. If it is almost time for the next dose, skip the missed dose and take the next scheduled dose at the appropriate time. A double dose should not be taken.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 Dosage Forms, Strengths and Composition

Route of Administration	Dosage Form/ Strength / Composition	Non-medicinal Ingredients
Oral	Tablet 5 mg, 10 mg, 20 mg, or 40 mg rosuvastatin (as rosuvastatin calcium)	Colloidal silicon dioxide, corn starch, ferric oxide red (for 10 mg, 20 mg and 40 mg) , ferric oxide yellow, hypromellose, lactose anhydrous, mannitol, microcrystalline cellulose, polyethylene glycol, sodium stearyl fumarate, talc, titanium dioxide

Sandoz Rosuvastatin (rosuvastatin calcium) 5 mg film-coated tablets are yellow, round, biconvex with “RSV 5” debossed on one side.

Sandoz Rosuvastatin 10 mg film-coated tablets are brown, round with “RSV 10” debossed on one side.

Sandoz Rosuvastatin 20 mg film-coated tablets are brown, round with “RSV 20” debossed on one side.

Sandoz Rosuvastatin 40 mg film-coated tablets are brown, round with “RSV 40” debossed on one side.

Packaging
Sandoz Rosuvastatin 5 mg, 10 mg, 20 mg tablets are available as blisters with 30 tablets per box, and as bottles of 100 and bottles of 500 tablets.

Sandoz Rosuvastatin 40 mg tablets is available as blisters with 30 tablets per box, and as bottles of 100 tablets

7 WARNINGS AND PRECAUTIONS

General

The patient should be advised to inform subsequent health professionals of the prior use of Sandoz 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.

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 8 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.

Genetic Polymorphism: In patients with SLCO1B1 (OATP1B1) and/or ABCG2 (BCRP) genetic polymorphisms there is a risk of increased rosuvastatin exposure (see 9 DRUG INTERACTIONS and 10.3 Pharmacokinetics, Special Populations and Conditions).

Hepatic/Biliary/Pancreatic

Hepatic Effects: 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 Sandoz Rosuvastatin or if the patient is titrated to the dose of 40 mg.

Sandoz 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 8.5 Post-Market Adverse Reactions). If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with Sandoz Rosuvastatin, promptly interrupt therapy. If an alternate etiology is not found, do not restart Sandoz 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 4.2 Recommended Dose and Dosage Adjustment, Patients with Hepatic Impairment).

Musculoskeletal

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.

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

- persistent 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
- positive anti-HMG CoA reductase antibody

Pre-disposing Factors for Myopathy/Rhabdomyolysis

Sandoz 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 2 CONTRAINDICATIONS, 9 DRUG INTERACTIONS, 4 DOSAGE AND ADMINISTRATION and 10.3

Pharmacokinetics, Special Populations and Conditions).

Statins may in rare instances induce or aggravate myasthenia gravis or ocular myasthenia (see 8.5 Post-Market Adverse Reactions) including reports of recurrence when the same or a different statin was administered. Sandoz Rosuvastatin should be used with caution in patients with these conditions and should be discontinued if they are induced or aggravated.

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.

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, Sandoz Rosuvastatin 40 mg is contraindicated in these patients (see 2 CONTRAINDICATIONS and 4.2 Recommended Dose and Dosage Adjustment, 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 calcium-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 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.

Reproductive Health: Female and Male Potential

Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Sandoz 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. 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 7.1.1 Pregnant Women and 7.1.2 Breast-feeding).

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 (see 2 CONTRAINDICATIONS).

7.1 Special Populations

Ethnic Origin

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 10.3 Pharmacokinetics, Ethnic Origin, 2 CONTRAINDICATIONS and 4.2 Recommended Dose and Dosage Adjustment, Ethnic Origin).

7.1.1 Pregnant Women

Sandoz Rosuvastatin is contraindicated during pregnancy (see 2 CONTRAINDICATIONS).

7.1.2 Breast-feeding

It is not known whether rosuvastatin is excreted in human milk. Because of the potential for adverse reactions in nursing infants, women taking Sandoz Rosuvastatin should not breast-feed (see 2 CONTRAINDICATIONS).

7.1.3 Pediatrics

Pediatrics (10 – <18 years of age): Elevations in serum creatine phosphokinase (CK) > 10 x ULN were observed more frequently in pediatric patients treated with rosuvastatin calcium compared with placebo. CK elevation > 10 x ULN (with or without muscle symptoms) was more frequent with increasing rosuvastatin calcium dose (see 8.2.1 Clinical Trial Adverse Reactions – Pediatrics).

The evaluation of linear growth (height), weight, BMI (body mass index), and secondary characteristics of sexual maturation by Tanner staging in boys and girls who are at least one year post-menarche (10 to 17 years of age) with heterozygous familial hypercholesterolemia treated with rosuvastatin was limited to a one-year period. Although endocrinology function, such as hormone disturbances, was not assessed, rosuvastatin had no detectable effect on growth or sexual maturation. The effects on menstrual cycle were not assessed. Rosuvastatin calcium doses greater than 20 mg have not been studied in this patient population (see 8.2.1 Clinical Trial Adverse Reactions – Pediatrics, 14 CLINICAL TRIALS, Pediatrics and 4.2 Recommended Dose and Dosage Adjustment, Pediatrics (10 – 17 years of age).

Adolescent females should be counselled on appropriate contraceptive methods while on Sandoz Rosuvastatin therapy (see 2 CONTRAINDICATIONS and 7.1.1 Pregnant Women). Treatment experience with rosuvastatin calcium in pediatric patients (aged 8 years and above) with homozygous familial hypercholesterolemia is limited to 8 patients.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): There were no clinically significant pharmacokinetic differences between young and elderly patients (≥ 65 years) (see 4.2 Recommended Dose and Dosage Adjustment, Use in Elderly). However, elderly patients may be more susceptible to myopathy (see 7 WARNINGS AND PRECAUTIONS, Musculoskeletal, Pre-disposing Factors for Myopathy/Rhabdomyolysis).

8 ADVERSE REACTIONS

8.1 Adverse 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.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from

clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Short-term Controlled Trials
Short-term controlled trials involved 1290 adult 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 2.

Table 2 Number (%) of Subjects with Associated Adverse Events Occurring with ≥ 1% Incidence in any Treatment Group: Placebo Controlled Pool

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

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: 14 CLINICAL TRIALS) involving 17,802 adult 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 3.

Table 3 Number (%) of Subjects with Treatment Emergent Adverse Events Regardless of Causality Occurring with ≥ 1% Incidence and > than Placebo: JUPITER

Body System/ Adverse Event	**Total Rosuvastatin Calcium 20 mg n = 8901 (%)**	**Placebo n = 8901 (%)**
Blood		
Anemia	2.2	2.1
Cardiac		
Palpitations	1.0	0.9
Gastrointestinal		
Diarrhea	4.7	4.6
Constipation	3.3	3.0
Nausea	2.4	2.3
General disorders		
Edema peripheral	3.7	3.0
Fatigue	3.7	3.5
Hepatobiliary		
Cholelithiasis	1.0	0.9
Infections		
Urinary tract	8.7	8.6
Nasopharyngitis	7.6	7.2
Bronchitis	7.2	7.1
Sinusitis	4.0	3.7
Influenza	4.0	3.6
Lower Respiratory tract	2.9	2.7
Gastroenteritis	1.9	1.7
Herpes zoster	1.6	1.4
Injury		
Contusion	1.7	1.4
Investigation		
ALT increased	1.4	1.0
Blood glucose increased	1.0	0.7
Metabolism		

Body System/ Adverse Event	Total Rosuvastatin Calcium 20 mg n = 8901 (%)	Placebo n = 8901 (%)
Diabetes mellitus	3.0	2.5
Musculoskeletal		
Back pain	7.6	6.9
Myalgia	7.6	6.6
Arthritis	5.8	5.6
Arthralgia	3.8	3.2
Muscle spasms	3.6	3.2
Osteoarthritis	1.8	1.4
Bursitis	1.5	1.3
Neck pain	1.1	1.0
Osteoporosis	1.0	0.8
Neoplasms		
Basal cell carcinoma	1.0	0.9
Psychiatric		
Insomnia	2.5	2.3
Renal		
Hematuria	2.4	2.0
Proteinuria	1.4	1.3
Respiratory		
Epistaxis	1.0	0.8

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Pediatrics (10 - <18 years of age)

The safety profile of rosuvastatin calcium in pediatric patients (boys and girls who are at least one year post-menarche, 10-<18 years of age with heterozygous familial hypercholesterolemia) is similar to adults although CK elevations > 10 x ULN (with or without muscle symptoms) were observed more frequently in a clinical trial of pediatric patients.

Rosuvastatin calcium was evaluated in a multicentre double-blind, placebo-controlled study of pediatric patients with heterozygous familial hypercholesterolemia. During the 12-week double-blind phase (n=176), patients were randomized to rosuvastatin calcium 5 mg, 10 mg or 20 mg or placebo. Four of 130 (3.0%) pediatric patients treated with rosuvastatin calcium (2 treated with 10 mg and 2 treated with 20 mg) had increased CK > 10 x ULN compared to 0 of 46 patients on placebo. Myopathy was reported in 2 patients receiving rosuvastatin calcium, one on 10 mg and one on 20 mg. During the 40 - week open label titration-to-goal phase of the study (n=173), 122 of 173 patients were titrated to rosuvastatin calcium 20 mg; 4 of the 173 (2.3%) pediatric patients treated with rosuvastatin calcium 20 mg had increased CK > 10 x ULN (with or without muscle

symptoms). All patients with CK elevations either continued treatment or resumed treatment after an interruption.

Myalgia was reported in 4 of the 130 (3.0%) pediatric patients treated with rosuvastatin calcium (1 treated with 5 mg, 1 treated with 10 mg and 2 treated with 20 mg) compared with 0 of 46 on placebo in the 12-week double-blind phase. In the 40-week open label titration-to-goal phase, myalgia was reported in 5 of 173 (2.9%) pediatric patients treated with rosuvastatin calcium.

Mean change in ALT and AST values from baseline were slightly higher in the rosuvastatin calcium group versus placebo; however, were not considered to be clinically significant. One patient, experienced an ALT elevation > 3 x ULN which returned to normal subsequent to an interruption in treatment.

Two adverse events of depression were reported in pediatric patients treated with rosuvastatin calcium 20 mg, one of which was determined to be causally related to treatment by the investigator.

Not all adverse reactions that have been identified in the adult populations have been observed in the clinical trials of pediatric patients. However, the same warnings and precautions for use and adverse events in adults also apply to pediatric patients (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS).

8.3 Less Common Clinical Trial Adverse 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%):

Endocrine disorders: diabetes mellitus

Gastrointestinal disorders: dyspepsia, gastroesophageal reflux disease, nausea

General disorders and administration site conditions: general pain

Hepatobiliary disorders: abnormal hepatic function ALT increase

Investigations: creatinine increase, creatine phosphokinase increase, hepatic enzyme increase

Musculoskeletal and connective tissue disorders: muscle weakness

Nervous system disorders: insomnia, paraesthesia, tremor, vertigo

Skin and subcutaneous tissue disorders: pruritus, rash, urticaria

Rare (≥ 0.01% and < 0.1%):

Immune system disorders: hypersensitivity reactions including angioedema

Musculoskeletal and connective tissue disorders: myopathy (including myositis), rhabdomyolysis

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

Gastrointestinal disorders: flatulence, gastroenteritis

General disorders and administration site conditions: accidental injury, chest pain

Infections and infestations: flu syndrome, infection, pharyngitis, rhinitis, urinary tract infection

Nervous system disorders: hypertonia

Respiratory, thoracic and mediastinal disorders: increased cough.

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

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

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 calcium (see 7 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 7 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.

8.5 Post-Market Adverse 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.

Endocrine disorders: Increases in fasting glucose and HbA1c levels

Eye disorders: ocular myasthenia (frequency: unknown)

Hematological disorders: Thrombocytopenia (frequency: unknown)

Hepatobiliary/Pancreatic disorders: pancreatitis (frequency: rare); jaundice, hepatitis (frequency: very rare)

Musculoskeletal disorders : arthralgia, immune-mediated necrotizing myopathy (frequency: very rare); myasthenia gravis (frequency: unknown)

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 7 WARNINGS AND PRECAUTIONS, Musculoskeletal).

Nervous system disorders: memory loss (frequency: very rare) ; peripheral neuropathy (frequency: unknown)

Reproductive system and breast disorders: gynecomastia (frequency: very rare)

Skin and subcutaneous tissue disorders: drug reaction with eosinophilia and systemic symptoms (DRESS), lichenoid drug eruption (frequency: unknown)

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.

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).

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- Concomitant treatment with cyclosporine (see 9.4 Drug-Drug Interactions)
- Concomitant treatment with sofosbuvir/velpatasvir/voxilaprevir (see 9.4 Drug-Drug Interactions)

9.2 Drug Interactions Overview

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 4). Stop using Sandoz Rosuvastatin or dose adjust depending on the level of effect on rosuvastatin exposure (see 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS and 4 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 Sandoz Rosuvastatin with

medicines that are inhibitors of these transporter proteins may result in increased rosuvastatin plasma concentrations and an increased risk of myopathy (see 7 WARNINGS AND PRECAUTIONS, 4 DOSAGE AND ADMINISTRATION, Dosing Considerations in Special Populations and Table 4).

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 7 WARNINGS AND PRECAUTIONS, Musculoskeletal, Pre-disposing Factors for Myopathy/Rhabdomyolysis). Therefore, combined drug therapy should be approached with caution.

Concomitant Therapies Without Clinically Significant Interactions

Bile Acid Sequestrants: Sandoz 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 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.

9.3 Drug-Behavioural Interactions

Interactions with behavioural risks have not been established.

9.4 Drug-Drug Interactions

The drugs listed in Table 4 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 4 Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Antacids	CT	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 Sandoz Rosuvastatin at a time of day when they are less likely to need the antacid.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Capmatinib	CT	Coadministration of rosuvastatin calcium 10 mg (single dose) and capmatinib 400 mg (BID) to adult patients with mesenchymal-epithelial transition-dysregulated advanced solid tumours resulted in a 2.08-fold increase in the mean AUC of rosuvastatin.	The dose of Sandoz Rosuvastatin should not exceed 20 mg daily when used concomitantly with capmatinib.
Clopidogrel	CT	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 Sandoz Rosuvastatin should not exceed 20 mg daily when used concomitantly with clopidogrel.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Coumarin Anticoagulants	CT	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 calcium 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 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.
Darolutamide	CT	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 Cmax.	For coadministration, the dose of Sandoz Rosuvastatin should not exceed 5 mg once daily.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Dronedarone	CT	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 Sandoz Rosuvastatin should not exceed 20 mg daily when used concomitantly with dronedarone.
Eltrombopag	CT	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 Sandoz Rosuvastatin should not exceed 20 mg daily when used concomitantly with eltrombopag.
Enasidenib	CT	Coadministration of enasidenib (100 mg, OD for 28 days) and rosuvastatin calcium 10 mg (single dose) in patients with relapsed or refractory acute myeloid leukemia or myelodysplastic syndrome resulted in a 2.4-fold increase in the AUC of rosuvastatin.	The dose of Sandoz Rosuvastatin should not exceed 10 mg daily when used concomitantly with enasidenib.
Febuxostat	CT	Coadministration of rosuvastatin calcium 10 mg (single dose) and febuxostat 120 mg (OD) to healthy volunteers resulted in a 1.9-fold increase in the mean AUC of rosuvastatin.	The dose of Sandoz Rosuvastatin should not exceed 20 mg daily when used concomitantly with febuxostat.
Fostamatinib	CT	Coadministration of rosuvastatin calcium 20 mg (single dose) and fostamatinib 100 mg (BID) to healthy volunteers resulted in a 1.96-fold increase in the mean AUC of rosuvastatin.	The dose of Sandoz Rosuvastatin should not exceed 20 mg daily when used concomitantly with fostamatinib.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Fusidic Acid	C	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.	Coadministration of Sandoz Rosuvastatin with fusidic acid should be avoided. Temporary suspension of Sandoz Rosuvastatin treatment may be appropriate when the use of fusidic acid is necessary.
Gemfibrozil	CT	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 Cmax and mean AUC of rosuvastatin respectively.	Due to an observed increased risk of myopathy/ rhabdomyolysis, combination therapy with Sandoz Rosuvastatin and gemfibrozil should be avoided. If used together, the dose of Sandoz Rosuvastatin should not exceed 20 mg once daily.
Immunosuppressants (Including Cyclosporine)	CT	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 (Cmax) and 7.1-fold (AUC[0-24]) compared with historical data in healthy individuals.	The concomitant use of Sandoz Rosuvastatin and cyclosporine is contraindicated (see 2 CONTRAINDICATIONS).

Proper/Common name	Source of Evidence	Effect	Clinical comment
Itraconazole	CT	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 calcium.	The dose of Sandoz Rosuvastatin should not exceed 20 mg daily when used concomitantly with itraconazole.
Oral Contraceptives	CT	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.
Protease Inhibitors	CT	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:	
	CT	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).	For coadministration with atazanavir/ritonavir, the dose of Sandoz Rosuvastatin should not exceed 10 mg daily.

Proper/Common name	Source of Evidence	Effect	Clinical comment
	CT	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 the dose of Sandoz Rosuvastatin should not exceed 20 mg daily.
	CT	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 Sandoz Rosuvastatin should not exceed 10 mg daily.
	CT	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 10 mg (single dose); approximately 2.26- fold increase in rosuvastatin AUC.	For coadministration, the dose of Sandoz Rosuvastatin should not exceed 10 mg daily with grazoprevir/elbasvir and 20 mg daily with grazoprevir alone.
	CT	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).	For coadministration with lopinavir/ritonavir, the dose of Sandoz Rosuvastatin should not exceed 20 mg daily.

Proper/Common name	Source of Evidence	Effect	Clinical comment
	CT	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 Cmax and AUC in three direct-acting antiviral agents (3D) and 2.61-fold and 1.32-fold increases for Cmax and AUC in two direct-acting antiviral agents (2D) treatment.	For coadministration, the dose of Sandoz Rosuvastatin should not exceed 10 mg daily in combination with 3D treatment and 20 mg daily for combination with 2D treatment.
	CT	Simeprevir 150 mg (OD, 7 days), rosuvastatin calcium 10 mg (single dose); approximately a 3.2-fold increase in rosuvastatin Cmax and 2.8-fold increase in rosuvastatin AUC.	For coadministration, the dose of Sandoz Rosuvastatin should not exceed 10 mg daily.
	CT	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 Sandoz Rosuvastatin with sofosbuvir/velpatasvir/ voxilaprevir is contraindicated (see 2 CONTRAINDICATIONS).
	CT	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).	For coadministration with tipranavir/ritonavir the dose of Sandoz Rosuvastatin should not exceed 20 mg daily.
	CT	Velpatasvir 100 mg OD, rosuvastatin calcium 10 mg (single dose); approximately 2.69-fold increase in	For coadministration, the dose of Sandoz Rosuvastatin should not exceed 10 mg daily.

Proper/Common name	Source of Evidence	Effect	Clinical comment
		rosuvastatin AUC.	
Regorafenib	CT	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 Cmax.	For coadministration, the dose of Sandoz Rosuvastatin should not exceed 10 mg daily.
Roxadustat	CT	Coadministration of Sandoz Rosuvastatin 10 mg (single dose) with Roxadustat 200 mg (QOD) to healthy volunteers; 2.0-fold increase in rosuvastatin AUC.	The dose of Sandoz Rosuvastatin should not exceed 10 mg daily when used concomitantly with Roxadustat.
Tafamidis	CT	Coadministration of Sandoz Rosuvastatin 10 mg (single-dose) with tafamidis 61 mg (BID on Days 1 & 2, followed by OD on Days 3 to 9) to healthy volunteers; 1,97-fold increase in the AUC of rosuvastatin.	The dose of Sandoz Rosuvastatin should not exceed 20 mg daily when used concomitantly with tafamidis.
Teriflunomide	CT	Coadministration of rosuvastatin calcium with teriflunomide can result in a 2.51-fold increase in the mean AUC of rosuvastatin.	The dose of Sandoz Rosuvastatin should not exceed 10 mg daily when used concomitantly with teriflunomide.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

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

If the expected increase in rosuvastatin exposure (AUC) is approximately 2-fold or higher, the starting dose of Sandoz Rosuvastatin should not exceed 5 mg once daily. The maximum daily dose

of Sandoz Rosuvastatin should be adjusted so that the expected rosuvastatin exposure would not likely exceed that of a 40 mg daily dose of Sandoz Rosuvastatin taken without interacting medicines (see 2 CONTRAINDICATIONS and Table 4).

Drug-drug interaction studies have not been performed in pediatric patients (boys and girls who are at least one year post-menarche, 10 to <18 years of age) with heterozygous familial hypercholesterolemia.

9.5 Drug-Food Interactions

Sandoz Rosuvastatin can be taken with or without food (see 4 DOSAGE AND ADMINISTRATION).

9.6 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

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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.

10.2 Pharmacodynamics

Epidemiologic, clinical and experimental studies have established that high LDL-C, low HDL-C and high plasma triglyceride (TG) promote human atherosclerosis and are risk factors for developing

cardiovascular disease. Some studies have also shown that the total cholesterol (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.

Human Pharmacology
Rosuvastatin calcium decreases elevated Total-C, LDL-C, TG and increases HDL- C in patients with homozygous and heterozygous 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 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.

10.3 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 (Cmax) 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. Sandoz 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.

Elimination
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 (t½) of rosuvastatin is approximately 19 hours and does not increase with increasing doses.

Special Populations and Conditions

- **Pediatrics (10 – <18 years of age):** There was no clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin in adults. The pharmacokinetics of rosuvastatin in pediatric patients 10 to 17 years of age with heterozygous familial hypercholesterolemia was similar to that of adult volunteers. Following single dose administration of rosuvastatin calcium 10 mg, the Cmax values in two studies of healthy adult volunteers were 5.8 ng/mL (n=12) and 3.8 ng/mL (n=18) compared to 6.3 ng/mL (n=6) in pediatric patients with heterozygous familial hypercholesterolemia. The AUC(0-t) values in healthy adult volunteers were 45.9 ng·h/mL (n=12) and 31.6 ng·h/mL (n=18) compared to 52.2 ng·h/mL in pediatric patients with heterozygous familial hypercholesterolemia.

- **Genetic Polymorphism:** 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.

- **Ethnic Origin:** 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 2 CONTRAINDICATIONS and 7.1 Special Populations, Ethnic Origin and see 4.2 Recommended Dose and Dosage Adjustment, Ethnic Origin).

11 STORAGE, STABILITY AND DISPOSAL

Store between 15°C and 30°C.

12 SPECIAL HANDLING INSTRUCTIONS

No special requirements.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

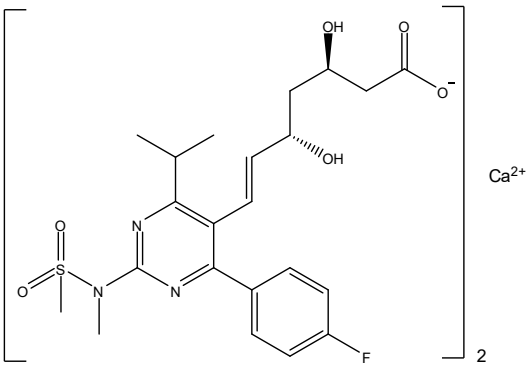
Drug Substance

Common Name: rosuvastatin calcium

Chemical Name: calcium (3*R*,5*S*,6*E*)-7-[4-(4-Fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)amino]-5-pyrimidinyl]-3,5-dihydroxy-6-heptenoat

Molecular Formula and Molecular Mass: $C_{44}H_{54}CaF_2N_6O_{12}S_2$ and 1001.14 g/mol

Structural Formula:



Physicochemical Properties: Rosuvastatin calcium is an almost white or yellowish-white powder, is slightly soluble in water and slightly soluble in ethanol. It has a pH 6.7 – 6.9 (1% w/v, 20°C). The characteristic angle of specific optical rotation (c = 0.5, 589 nm, 20°C) is between + 14.0° and + 20.0° (calculated to the anhydrous and solvent free substance).

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

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

Rosuvastatin 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.

Pediatrics (10 – <18 years of age)

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

The majority of pediatric patients, who met the study inclusion criteria, had a baseline LDL-C ≥ 4.9 mmol/L or LDL-C > 4.1 mmol/L and a positive family history of premature cardiovascular disease.

Rosuvastatin calcium significantly reduced LDL-C, total cholesterol and ApoB levels during the 12-week double-blind phase. Results are shown in Table 6.

[1] Defined as documented genetic defect in LDL receptor or ApoB by DNA analysis or documented evidence of familial hypercholesterolemia in a first-degree relative (i.e. LDL-C > 4.9 mmol/L in an adult not receiving a statin or LDL-C > 2.5 mmol/L in an adult receiving a statin; LDL-C > 4.1 mmol/L in a child < 18 years of age not receiving a statin or LDL > 2.1 mmol/L in a child < 18 years of age receiving a statin).

Table 6 Lipid-modifying effects of rosuvastatin calcium in pediatric patients with heterozygous familial hypercholesterolemia (least-squares mean percent change from baseline to week 12)

Rosuvastatin Calcium Dose (mg/day)	N	LDL-C *	HDL-C	Total-C *	TG	Non-HDL-C*	ApoB *	ApoA-1
Placebo	46	-0.7	6.9	-0.0	5.1	-0.9	-1.7	2.8
5	42	-38.3	4.2	-29.9	0.3	-36.1	-31.7	1.8
10	44	-44.6	11.2	-34.2	-13.6	-43.0	-38.1	5.4
20	44	-50.0	8.9	-38.7	-8.1	-47.5	-40.7	4.0

* $p < 0.001$ vs. placebo for all rosuvastatin calcium doses.

At the end of the 12-week double-blind phase, 12%, 41% and 41% of patients treated with rosuvastatin calcium 5, 10 and 20 mg, respectively, achieved an LDL-C of less than 2.8 mmol/L (110 mg/dL).

At the end of the 40-week, open label, titration to goal phase, dosing up to a maximum of 20 mg once daily, 70 of 173 patients (40.5%) had achieved an LDL-C of less than 2.8 mmol/L (110 mg/dL).

The long term efficacy of rosuvastatin calcium therapy in the treatment of pediatric patients has not been studied and has therefore not been demonstrated to reduce mortality or morbidity in adulthood.

During the 12-week double-blind phase, 4 of 130 (3.0%) pediatric patients treated with rosuvastatin calcium (2 treated with 10 mg and 2 treated with 20 mg) had increased CK > 10 x ULN compared to 0 of 46 patients on placebo. Myopathy was reported in 2 patients receiving rosuvastatin calcium, one on 10 mg and one on 20 mg. During the 40-week open label titration-to-goal phase of the study, 122 of 173 patients were titrated to rosuvastatin calcium 20 mg; 4 of the 173 (2.3%) pediatric patients treated with rosuvastatin calcium 20 mg had increased CK > 10 x ULN (with or without muscle symptoms). All patients with CK elevations either continued treatment or resumed treatment after an interruption.

Myalgia was reported in 4 of the 130 (3.0%) pediatric patients treated with rosuvastatin calcium (1 treated with 5 mg, 1 treated with 10 mg and 2 treated with 20 mg) compared with 0 of 46 on placebo in the 12-week placebo-controlled phase. In the 40-week open label titration-to-goal phase, myalgia was reported in 5 of 173 (2.9%) pediatric patients treated with rosuvastatin calcium.

After 52 weeks of study treatment, although endocrinology function, such as hormone disturbances, was not assessed, no effect on growth or sexual maturation was detected (see 7.1.3 Pediatrics).

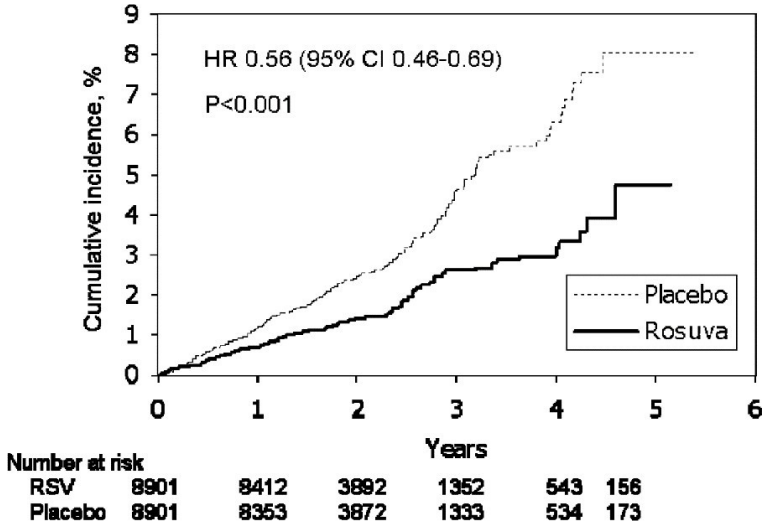
Prevention of Major Cardiovascular Events

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. Th e 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 HDL-C 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 calcium-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 7. 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 7 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.

14.2 Comparative Bioavailability Studies

A randomized, two-way, single-dose, crossover comparative bioavailability study of SANDOZ ROSUVASTATIN 40 mg tablets (Sandoz Canada Inc.) and [Pr]CRESTOR® 40 mg tablets (AstraZeneca Canada Inc.) was conducted in healthy, adult, male subjects under fasting conditions. Comparative bioavailability data from 30 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Rosuvastatin (1 x 40 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (pg·h/mL)	154025.01 169032.82 (45.40)	164672.35 179670.06 (42.82)	93.5	87.6 – 99.9
AUC_I (pg·h/mL)	161294.25 175834.14 (43.73)	169480.44 184341.83 (42.27)	95.2	89.2 – 101.5
C_{max} (pg/mL)	18171.91 19984.38 (45.86)	19035.16 21020.65 (43.55)	95.5	87.3 – 104.4
T_{max}[3] (h)	4.27 (16.75)	3.95 (27.09)		
$T_{½}$[4] (h)	20.18 (69.62)	17.55 (32.79)		

[1] SANDOZ ROSUVASTATIN (rosuvastatin calcium) tablets, 40 mg (Sandoz Canada Inc.)
[2] [Pr]CRESTOR® (rosuvastatin calcium) tablets, 40 mg (AstraZeneca Canada Inc.)
[3] Expressed as the median (range) only
[4] Expressed as the arithmetic mean (CV %) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General 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 9 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 10 below.

Table 10 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 11 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 11 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)	Cmax (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				

			Margin vs. NOAEL: 40 mg	
Species/Finding	**No-Effect Dose (mg/kg/day)**	**Minimal Toxic Dose (mg/kg/day)**	**Cmax (adjusted for protein binding (ng/mL)**	**AUC (adjusted for protein binding) (ng•h/mL)**
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

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.

Genotoxicity

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.

Reproductive and Developmental Toxicology

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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. PrCRESTOR® (Tablets, 5, 10, 20 and 40 mg), submission control 260266, Product Monograph, AstraZeneca Canada Inc.(Jun 8, 2022).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr SANDOZ ROSUVASTATIN
Rosuvastatin Calcium Tablets

Read this carefully before you start taking **Sandoz Rosuvastatin** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Sandoz Rosuvastatin.**

What is Sandoz Rosuvastatin used for?
Sandoz Rosuvastatin is used along with a change in diet to lower the level of cholesterol and other fats (such as triglycerides) in the blood in:

- adults with high blood cholesterol. In these adults, changes in diet and exercise alone were not effective in lowering their blood cholesterol.
- boys and girls (who have had their period for at least a year) who are 10 to less than 18 years of age with heterozygous familial hypercholesterolemia. This is a genetic condition where high blood cholesterol is inherited from one of the parents. In these children, a change in diet alone was not effective in lowering their blood cholesterol.

Sandoz Rosuvastatin is also used in adults who have no history of heart attack or stroke but who have two or more risk factors as determined by their healthcare professional to reduce the risk of:

- heart attack
- stroke
- undergoing a procedure called coronary artery revascularization. This is a medical procedure used to treat severely blocked arteries due to plaque buildup caused by high blood cholesterol levels.

How does Sandoz Rosuvastatin work?
Sandoz Rosuvastatin belongs to a class of medicines known as "statins", more specifically called HMG-CoA reductase inhibitors. Statins block an enzyme called HMG-CoA reductase in your liver, which is involved in the production of cholesterol in your body. Statins are used along with changes to diet and exercise to help control the amount of cholesterol produced by the body.

Sandoz 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.

If levels of bad 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. By reducing bad cholesterol levels, Sandoz Rosuvastatin reduces the risk of heart attack or stroke in adults who have risk factors, and reduces their risk of undergoing a serious medical procedure to treat severely blocked arteries due to plaque buildup.

What are the ingredients in Sandoz Rosuvastatin?
Medicinal ingredient: Rosuvastatin calcium
Non-medicinal ingredients: Colloidal silicon dioxide, corn starch, ferric oxide red, ferric oxide yellow, hypromellose, lactose anhydrous, mannitol, microcrystalline cellulose, polyethylene glycol, sodium stearyl fumarate, talc, titanium dioxide

Sandoz Rosuvastatin comes in the following dosage forms:
Tablets: 5 mg, 10 mg, 20 mg and 40 mg rosuvastatin.

Do not use Sandoz Rosuvastatin if you/your child:

- are allergic to rosuvastatin or any other ingredients in Sandoz Rosuvastatin or its packaging.
- currently have liver disease or unexplained increases in liver enzymes.
- are pregnant or think you might be pregnant.
- are breast-feeding.
- are taking cyclosporine (used to suppress your immune system).
- are taking sofosbuvir/velpatasvir/voxilaprevir (used to treat hepatitis C infection).

Do not use the **40 mg tablet** if you:

- are of Asian descent.
- have risk factors for muscle problems. This includes if you:
  - have had or have a family history of muscular disorders.
  - had any past problems with muscles (pain, tenderness) after using statins such as atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin or simvastatin.
  - currently take fibrates (such as gemfibrozil, fenofibrate and bezafibrate) or niacin (nicotinic acid) (used to lower fat levels in the blood).
  - have thyroid problems.
  - regularly drink **three or more** alcoholic drinks daily.
  - do excessive physical exercise.
  - are above 70 years of age.
  - have liver or kidney problems.
  - have diabetes accompanied with excess fat build-up in your liver.
  - had surgery or other tissue injury.
  - have a condition that causes weakness or frailty.
  - have any conditions or take any medicines that may increase the level of Sandoz Rosuvastatin in the blood. Talk to your healthcare professional if you are unsure.

To help avoid side effects and ensure proper use, talk to your/your child's healthcare professional before you/your child takes Sandoz Rosuvastatin. Talk about any health conditions or problems you/your child may have, including if you:

- have taken Sandoz Rosuvastatin or any other cholesterol-lowering medicines in the past.

- have heart problems.
- have high blood sugar or diabetes, or are at risk for diabetes.
- have been told that you/your child have genetic variations for the SLCO1B1 and/or ABCG2 genes. This may increase the level of Sandoz Rosuvastatin in the blood.
- have a history of liver problems.
- are of Asian descent.
- have risk factors for muscle problems (see section "**Do not use Sandoz Rosuvastatin if**" for details). Your healthcare professional will evaluate your medical condition and decide if you should take Sandoz Rosuvastatin 40 mg.
- have or have had myasthenia (a disease with general muscle weakness including the eye muscles and in some cases muscles used when breathing) as statins may aggravate the condition.

Other warnings you should know about:

Sandoz Rosuvastatin can cause serious side effects, including:

- **Hyperglycemia** (high blood sugar): This may lead to the development of diabetes. Your healthcare professional will monitor your blood sugar level regularly. If you have diabetes, closely monitor your blood sugar while taking Sandoz Rosuvastatin and report any unusual results to your healthcare professional.

- Muscle disorders such as:
  - **Myalgia** (muscle pain)
  - **Rhabdomyolysis** (breakdown of damaged muscle)
  - **Immune-Mediated Necrotizing Myopathy (IMNM)** (a type of autoimmune disease that causes muscle cell death)

  Tell your healthcare professional **right away** if you have any muscle pain, tenderness, soreness or weakness while taking Sandoz Rosuvastatin.

See the **Serious side effects and what to do about them** table for more information on these and other serious side effects.

Pregnancy:
- Sandoz Rosuvastatin should **not** be taken during pregnancy. It could harm an unborn baby. Your healthcare professional will discuss the potential risks with you.
- If you are a woman who could become pregnant, your healthcare professional will ask you to use a highly effective birth control method while taking Sandoz Rosuvastatin.
- If you discover that you are pregnant while taking Sandoz Rosuvastatin, **stop** taking the medicine and contact your healthcare professional **as soon as possible**.

Breastfeeding:
- It is not known if Sandoz Rosuvastatin can pass into breast milk and harm a breastfed baby. As such, Sandoz Rosuvastatin should **not** be taken while breastfeeding.

- Talk to your healthcare professional about the best way to feed your baby while you are taking Sandoz Rosuvastatin.

Check-ups and testing: Your healthcare professional may do blood tests before you start Sandoz Rosuvastatin and during your treatment. These tests will check:

- the level of CoQ10 (an antioxidant) in your blood.
- the amount of sugar (glucose) in your blood.
- that your liver or muscles are working properly.
- the amount of cholesterol and other fats in your blood.

Depending on your test results, your healthcare professional may adjust your dose, temporarily stop or discontinue your treatment with Sandoz Rosuvastatin.

Your healthcare professional may ask you to do a genetic test if you experience side effects while taking Sandoz Rosuvastatin. This test will determine if the side effects you are experiencing are due to your genes. These may affect the way your body processes Sandoz Rosuvastatin.

Tell your healthcare professional about all the medicines you/your child takes, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions

Do not take Sandoz Rosuvastatin with:

- cyclosporine (used to suppress the immune system).
- sofosbuvir/velpatasvir/voxilaprevir (used to treat hepatitis C infection).

Taking Sandoz Rosuvastatin with any of these medicines may cause serious drug interactions. Ask your healthcare professional if you are unsure you are taking them.

The following may also interact with Sandoz Rosuvastatin:

- medicines used to lower blood cholesterol. This includes other statins (e.g., atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin), fibrates (e.g., gemfibrozil, fenofibrate, bezafibrate), niacin (nicotinic acid), ezetimibe.
- medicines used to treat viral infections such as HIV/AIDS and hepatitis C. This includes antiviral medicines alone or in combination with atazanavir, ritonavir, lopinavir, ombitasvir, paritaprevir, dasabuvir, simeprevir, velpatasvir, grazoprevir, elbasvir, glecaprevir, pibrentasvir, darunavir, tipranavir.
- ketoconazole, fluconazole, itraconazole (used to treat fungal infections).
- spironolactone (used to treat high blood pressure).
- cimetidine (used to treat ulcers of the stomach and intestines).
- dronedarone (used to treat abnormal heart rhythms).
- regorafenib, darolutamide, capmatinib (used to treat cancer).
- febuxostat (used to treat and prevent high blood levels of uric acid).
- fostamatinib, eltrombopag (used to treat low blood platelets).
- teriflunomide (used to treat relapsing remitting multiple sclerosis).

- warfarin, clopidogrel (used to prevent blood clots).
- frequent use of antacids (used to treat heartburn). Sandoz Rosuvastatin should be taken 2 hours apart.
- fusidic acid (used to treat bacterial infections). Your healthcare professional may temporarily stop your treatment with Sandoz Rosuvastatin until your treatment with fusidic acid is complete.
- birth control pills.
- baicalin (a herbal product).
- roxadustat (medicine that increases the number of red blood cells and hemoglobin level in patients with chronic kidney disease)
- enasidenib (used to treat a condition called acute myeloid leukemia)
- tafamidis (used to treat a condition called transthyretin amyloidosis).

How to take Sandoz Rosuvastatin:
Your healthcare professional 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.

- Take Sandoz Rosuvastatin exactly as your healthcare professional tells you. Keep taking it even if you feel well.
- Take Sandoz Rosuvastatin once a day. Swallow each tablet whole with a drink of water.
- Remember to take Sandoz Rosuvastatin at the same time every day. Sandoz Rosuvastatin can be taken in the morning or evening, with or without food.
- Do not change the dose or stop taking the medicine without first talking to your healthcare professional.
- If you get sick, have an operation, or need medical treatment while taking Sandoz Rosuvastatin, let the healthcare professional or pharmacist know that you are taking Sandoz Rosuvastatin.
- If you have to see a different healthcare professional, for any reason, be sure to tell him/her of any medicines you might be taking, including Sandoz Rosuvastatin.

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

Sandoz Rosuvastatin is just part of the treatment the healthcare professional will plan with you to help keep you healthy. Depending on your health and lifestyle, the healthcare professional may recommend:

- a change in diet to:
  - control your weight.
  - reduce your intake of cholesterol and saturated fats.
- exercise that is right for you.
- quitting smoking or avoiding smoky places.
- giving up alcohol or drinking less.

Follow your healthcare professional's instructions carefully.

Usual dose:
The dose of Sandoz Rosuvastatin prescribed to you will depend on your medical condition and your blood cholesterol level.

To lower blood cholesterol
Adults:

- The recommended starting dose is 10 mg once daily. Some people may be asked to start treatment with 5 mg once a day while others may be asked to start with 20 mg once a day.
- After checking the amount of cholesterol and other fats in your blood, your healthcare professional may decide to adjust your dose until you are taking the amount of Sandoz Rosuvastatin that is right for you. The dosage range for Sandoz Rosuvastatin is 5 to 40 mg once a day.
- The maximum dose is 40 mg per day.

Children and adolescents (10 to less than 18 years of age):

- The recommended starting dose is 5 mg once daily.
- After checking the amount of cholesterol and other fats in your child's blood, the healthcare professional may decide to adjust your child's dose until they are taking the amount of Sandoz Rosuvastatin that is right for them.
- The maximum dose is 10 mg per day.

To lower the risk of heart attack, stroke or undergoing coronary artery vascularization
Adults: The recommended dose is 20 mg once daily.

Overdose:

If you think you, or a person you are caring for, have taken too much Sandoz Rosuvastatin, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to take a dose, take it as soon as you remember. If you do not remember until it is almost time for your next dose, skip the missed dose and take the next dose as scheduled. Do not take a double dose to make-up for a missed dose.

What are possible side effects from using Sandoz Rosuvastatin?
These are not all the possible side effects you may have when taking Sandoz Rosuvastatin. If you experience any side effects not listed here, tell your healthcare professional.

All medicines can cause unwanted side effects. These effects are usually mild and disappear after a short time.

Side effects may include:

- joint pain, swelling of the joints
- muscle spasms or stiffness, shaking (tremors)

- abdominal, chest or back pain
- feeling weak, lack of energy
- nausea, indigestion, constipation, diarrhea, gas
- swelling of the extremities (hands, arms, legs or feet)
- tingling sensation, numbness, weakness or pain in the hands, arms, legs or feet
- sinus infection, runny or stuffy nose
- flu (fever, headache, body aches, cough)
- cough, sore throat
- memory loss, confusion
- trouble sleeping or staying asleep, nightmares
- hives, skin rash or itch
- impotence (inability to get or keep an erection)
- blood in urine
- breast growth in males
- rash that may occur on the skin od scores in the mouth (lichenoid drug eruption)

Sandoz Rosuvastatin can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Allergic reactions: difficulty swallowing or breathing, wheezing; drop in blood pressure; feeling sick to your stomach and throwing up; hives or rash; severe itching; swelling of the face, lips, tongue or throat, blistering of the skin and mucous membranes of the lips, eyes, mouth, nasal passages or genitals, high body temperature and enlarged lymph nodes			✓
Liver failure (serious disturbance of liver function): yellow colour to skin, whites of the eyes (jaundice), bleeding easily, swollen abdomen, mental disorientation or confusion, sleepiness, coma.			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Muscle disorders: • **Myalgia** (muscle pain): aching muscles, tenderness or weakness that you cannot explain. • **Rhabdomyolysis** (breakdown of damaged muscle): muscle tenderness, weakness, red-brown (tea coloured) urine. • **Immune-Mediated Necrotizing Myopathy (IMNM)** (a type of autoimmune disease that causes muscle cell death): progressive muscle weakness in forearms, thighs, hips, shoulders, neck and back, difficulty standing up, climbing stairs or lifting arms over the head, falling and difficulty getting up from a fall, general feeling of tiredness. These muscle disorders can be accompanied with fever or feeling unwell.		✓ ✓	✓
Pancreatitis (inflammation of the pancreas): upper abdominal pain, fever, rapid heartbeat, nausea, vomiting, tenderness when touching the abdomen.		✓	
VERY RARE			
Hepatitis (inflammation of the liver): abdominal pain, fatigue, fever, itchiness, light coloured stool, trouble thinking clearly, yellowing of the skin.		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Interstitial lung disease (disease that inflames or scars lung tissue): shortness of breath when at rest that gets worse with exertion, dry cough.			✓
UNKNOWN FREQUENCY			
Depression (sad mood that won't go away): trouble sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family, gatherings and activities with friends, reduced sex drive and thoughts of death or suicide. If you have a history of depression, your depression may become worse.		✓	
Hyperglycemia (high blood sugar): increased thirst, frequent urination, dry skin, headache, blurred vision and fatigue.	✓		
Myasthenia gravis (muscle weakness): • **General:** difficulty in speaking, chewing and swallowing or weakness of arms and legs and in some cases muscles used when breathing. • **Ocular (eye):** weak, drooping eyelid(s) causing vision changes.			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Serious skin reactions: fever, severe rash, swollen lymph glands, blisters and peeling skin that may start in and around the mouth, nose, eyes and genitals and spread to other areas of the body, yellow skin or eyes.			✓
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) 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.

Storage:

- Store Sandoz Rosuvastatin at room temperature (15°C - 30°C).
- Keep out of reach and sight of children.

If you want more information about Sandoz Rosuvastatin:

- Talk to your healthcare professional.
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html or the manufacturer's website www.sandoz.ca or by calling 1-800-361-3062.

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