

**PRODUCT MONOGRAPH**

**Pr NOVO-ROSUVASTATIN**

Rosuvastatin as rosuvastatin calcium

Tablets, 5 mg, 10 mg, 20 mg and 40 mg

Professed Standard

LIPID METABOLISM REGULATOR

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## TABLE OF CONTENTS

<b>PART I: HEALTH PROFESSIONAL INFORMATION</b> .....	3
SUMMARY PRODUCT INFORMATION .....	3
INDICATIONS AND CLINICAL USE.....	3
CONTRAINDICATIONS .....	4
WARNINGS AND PRECAUTIONS.....	5
ADVERSE REACTIONS.....	10
DRUG INTERACTIONS .....	16
DOSAGE AND ADMINISTRATION.....	20
OVERDOSAGE .....	23
ACTION AND CLINICAL PHARMACOLOGY .....	23
STORAGE AND STABILITY.....	25
<b>PART II: SCIENTIFIC INFORMATION</b> .....	27
PHARMACEUTICAL INFORMATION.....	27
CLINICAL TRIALS.....	28
DETAILED PHARMACOLOGY .....	33
TOXICOLOGY .....	35
REFERENCES .....	39
<b>PART III CONSUMER INFORMATION</b> .....	41

**PrNOVO-ROSUVASTATIN**  
rosuvastatin calcium

**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablets: 5, 10, 20 and 40 mg	carmoisine aluminium lake (10 mg, 20 mg, 40 mg), crospovidone, indigo carmine aluminium lake (10 mg, 20 mg, 40 mg), iron oxide black (5 mg), iron oxide red (10 mg, 20 mg, 40 mg), iron oxide yellow, lactose anhydrous, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, sodium stearyl fumarate, sunset yellow FCF aluminum lake (5 mg), talc, and titanium dioxide.

**INDICATIONS AND CLINICAL USE**

**Hypercholesterolemia**

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

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

**Pediatrics (10 – 17 years of age)**

NOVO-ROSUVASTATIN is indicated as an adjunct to diet for the reduction of elevated total cholesterol (Total-C), LDL-C and ApoB in boys and girls who are at least one year post-menarche, 10 to 17 years of age with heterozygous familial hypercholesterolemia (see CLINICAL TRIALS), when response to diet alone has been inadequate.

### **Prevention of Major Cardiovascular Events**

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

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

### **CONTRAINDICATIONS**

NOVO-ROSUVASTATIN (rosuvastatin calcium) is contraindicated:

- In patients who are hypersensitive to any component of this medication (see DOSAGE FORMS, COMPOSITION AND PACKAGING).
- In patients with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal (see WARNINGS AND PRECAUTIONS).
- In pregnant and nursing women.

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

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

NOVO-ROSUVASTATIN **40 mg** is contraindicated in:

- Asian patients
- Patients with pre-disposing factors for myopathy/rhabdomyolysis such as:
  - Personal or family history of hereditary muscular disorders
  - Previous history of muscle toxicity with another HMG-CoA reductase inhibitor

- Concomitant use of a fibrate or niacin
- Severe hepatic impairment
- Severe renal impairment (CrCl < 30 mL/min/1.73m<sup>2</sup>) (see DOSAGE AND ADMINISTRATION, Patients with Renal Impairment)
- Hypothyroidism
- Alcohol abuse
- Situations where an increase in rosuvastatin plasma levels may occur (see DRUG INTERACTIONS and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

## **WARNINGS AND PRECAUTIONS**

### **General**

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

### **Cardiovascular**

#### **Co-enzyme Q<sub>10</sub> (ubiquinone)**

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

### **Endocrine and Metabolism**

#### **Endocrine Function**

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Rosuvastatin demonstrated no effect upon nonstimulated cortisol levels and no effect on thyroid metabolism as assessed by TSH plasma concentration. In rosuvastatin calcium-treated patients, there was no impairment of adrenocortical reserve and no reduction in plasma cortisol concentrations. Clinical studies with other HMG-CoA reductase inhibitors have suggested that

these agents do not reduce plasma testosterone concentration. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown.

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

### **Plasma Glucose**

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

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

### **Lipoprotein (a)**

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

### **Hepatic/Biliary/Pancreatic**

#### **Hepatic Effects**

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

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

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

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

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

## **Hepatic Impairment**

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

## **Muscle Effects**

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

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

Myopathy, defined as muscle pain or muscle weakness in conjunction with increases in creatine kinase (CK) values to greater than ten times the upper limit of normal, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness and/or marked elevation of CK. Patients should be advised to report promptly any unexplained muscle pain, tenderness or weakness, particularly if associated with malaise or fever. Patients who develop any signs or symptoms suggestive of myopathy should have their CK levels measured. Rosuvastatin calcium therapy should be discontinued if markedly elevated CK levels (> 10 x ULN) are measured or myopathy is diagnosed or suspected. There have been very rare reports of an immune-mediated necrotizing myopathy clinically characterized by persistent proximal muscle weakness and elevated serum creatine kinase during treatment or following discontinuation of statins, including rosuvastatin. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required.

### Pre-disposing factors for Myopathy/Rhabdomyolysis

Rosuvastatin calcium, as with other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

- Personal or family history of hereditary muscular disorders
- Previous history of muscle toxicity with another HMG-CoA reductase inhibitor

- Concomitant use of a fibrate or niacin
- Hypothyroidism
- Alcohol abuse
- Excessive physical exercise
- Age >70 years
- Renal impairment
- Hepatic impairment
- Diabetes with hepatic fatty change
- Surgery and trauma
- Frailty
- Situations where an increase in plasma levels of rosuvastatin may occur (see DRUG INTERACTIONS and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

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

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

## **Renal**

### **Renal Impairment**

Subjects with severe renal impairment ( $\text{CrCl} < 30 \text{ mL/min/1.73m}^2$ ) had a 3-fold increase in plasma concentration of rosuvastatin compared to healthy volunteers and, therefore, NOVOROSUVASTATIN 40 mg is contraindicated in these patients (see CONTRAINDICATIONS, and DOSAGE AND ADMINISTRATION, Patients with Renal Impairment).

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

During the clinical development program, dipstick-positive proteinuria and microscopic hematuria were observed among rosuvastatin-treated patients, predominantly in patients dosed above the recommended dose range (i.e. 80 mg). Abnormal urinalysis testing (dipstick-positive proteinuria) has been seen in patients taking rosuvastatin calcium and other HMG-CoA reductase inhibitors. This finding was more frequent in patients taking 40 mg when compared to lower doses of rosuvastatin or comparator statins. Shifts in urine protein from none or trace to ++ (dipstick) or more were seen in < 1% of patients at some time during treatment with 10 and 20 mg, and in approximately 3% of patients treated with 40 mg. The protein detected was mostly tubular in origin. In most cases, proteinuria was generally transient and it decreased or disappeared



spontaneously on continued therapy. It has not been shown to be predictive of acute or progressive renal disease.

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

### **Sensitivity/Resistance**

#### **Hypersensitivity**

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

### **Special Populations**

#### **Pregnant Women:**

**NOVO-ROSUVASTATIN is contraindicated during pregnancy (see CONTRAINDICATIONS).**

#### **Nursing Women:**

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

#### **Pediatrics (10 – 17 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 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 calcium was limited to a one-year period. Although endocrinology function, such as hormone disturbances, was not assessed, rosuvastatin calcium 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 ADVERSE

REACTIONS, Pediatrics, CLINICAL TRIALS, Pediatrics and DOSAGE AND ADMINISTRATION, Pediatrics).

Adolescent females should be counselled on appropriate contraceptive methods while on rosuvastatin calcium therapy (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women).

Treatment experience with rosuvastatin calcium in pediatric patients (aged 8 years and above) with homozygous familial hypercholesterolemia is limited to 8 patients.

### **Geriatrics (≥ 65 years of age):**

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

### **Race:**

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

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

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

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

### **Clinical Trial Adverse Drug Reactions**

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

**Adults**

Short-term Controlled Trials

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

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

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

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

Long-term Controlled Morbidity and Mortality Trials

In the **Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER)** study (see Part II: CLINICAL TRIALS) involving 17,802 participants treated with rosuvastatin calcium 20 mg once daily (n=8901) or placebo (n=8901), rosuvastatin calcium 20 mg was generally well tolerated. Subjects were followed for a mean duration of 2 years.

Discontinuation of therapy due to an adverse event occurred in 5.6% of subjects treated with rosuvastatin calcium and 5.5% of subjects treated with placebo. The most common adverse events that led to discontinuation from the study were: myalgia, arthralgia, abdominal pain and constipation. The associated adverse reaction reported in  $\geq 1\%$  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  $\geq 1\%$  and at a rate greater than placebo in patients participating in the JUPITER trial are shown in Table 2.

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

<b>Body System/ Adverse Event</b>	<b>Placebo (%) (N=8901)</b>	<b>Total rosuvastatin 20 mg (%) (N=8901)</b>
<b>Blood</b>		
Anemia	2.1	2.2
<b>Cardiac</b>		
Palpitations	0.9	1.0
<b>Gastrointestinal</b>		
Diarrhea	4.6	4.7
Constipation	3.0	3.3
Nausea	2.3	2.4
<b>General disorders</b>		
Edema peripheral	3.0	3.7
Fatigue	3.5	3.7
<b>Hepatobiliary</b>		
Cholelithiasis	0.9	1.0
<b>Infections</b>		
Urinary tract	8.6	8.7
Nasopharyngitis	7.2	7.6
Bronchitis	7.1	7.2
Sinusitis	3.7	4.0
Influenza	3.6	4.0
Lower Respiratory tract	2.7	2.9
Gastroenteritis	1.7	1.9
Herpes zoster	1.4	1.6
<b>Injury</b>		
Contusion	1.4	1.7
<b>Investigation</b>		
ALT increased	1.0	1.4
Blood glucose increased	0.7	1.0
<b>Metabolism</b>		
Diabetes mellitus	2.5	3.0
<b>Musculoskeletal</b>		
Back pain	6.9	7.6
Myalgia	6.6	7.6
Arthritis	5.6	5.8
Arthralgia	3.2	3.8
Muscle spasms	3.2	3.6
Osteoarthritis	1.4	1.8

	Bursitis	1.3	1.5
	Neck pain	1.0	1.1
	Osteoporosis	0.8	1.0
<b>Neoplasms</b>			
	Basal cell carcinoma	0.9	1.0
<b>Psychiatric</b>			
	Insomnia	2.3	2.5
<b>Renal</b>			
	Hematuria	2.0	2.4
	Proteinuria	1.3	1.4
<b>Respiratory</b>			
	Epistaxis	0.8	1.0

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

The frequency of adverse events in all clinical trials and considered possibly, probably or definitely drug related are as follows:

Uncommon ( $\geq 0.1\%$  and  $< 1\%$ ): Pruritus, rash, urticaria, arthralgia, muscle weakness, arthritis, constipation, nausea, dyspepsia, gastroesophageal reflux disease, ALT increase, creatine phosphokinase increase, hepatic enzyme increase, creatinine increase, paraesthesia, tremor, general pain, proteinuria, sinusitis, insomnia, abnormal hepatic function, vertigo, diabetes mellitus.

Rare ( $\geq 0.01\%$  and  $< 0.1\%$ ): Myopathy (including myositis), rhabdomyolysis, and hypersensitivity reactions including angioedema.

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

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

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

### **Abnormal Hematologic and Clinical Chemistry Findings**

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

Abnormal urinalysis testing (dipstick-positive proteinuria) has been seen in a small number of patients taking rosuvastatin calcium and other HMG-CoA reductase inhibitors. The protein detected was mostly tubular in origin. In most cases, proteinuria decreases or disappears

spontaneously on continued therapy and is not predictive of acute or progressive renal disease (see WARNINGS and PRECAUTIONS, Renal).

In the JUPITER trial, occurrences of diabetes mellitus as a pre-specified secondary outcome were reported more frequently in the rosuvastatin calcium-treated patients (2.8%) than in placebo (2.3%) and a slight increase in the number of subjects whose fasting glucose levels increased to  $\geq 5.6$  mmol/L (126 mg/dL) was observed in subjects treated with rosuvastatin calcium. 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.

### **Pediatrics (10 - 17 years of age)**

The safety profile of rosuvastatin calcium in pediatric patients (boys and girls who are at least one year post-menarche, 10-17 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 WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).

### **Post-Market Adverse Drug Reactions**

Because post-market reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. In addition to the events reported above, the following adverse events have been reported during post-marketing experience with rosuvastatin calcium, regardless of causality assessment.

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

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

Hepatobiliary disorders: Very rare: jaundice, hepatitis

Nervous system disorders: Very rare: memory loss

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

Other: Rare: pancreatitis; Very rare: gynecomastia

The following adverse events have been reported with some statins:

Sleep Disturbances, including insomnia and nightmares.

Mood related disorders including depression.

Fatal and non-fatal hepatic failure.

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

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

There have been rare post-marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally non-serious and reversible upon

statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

## **DRUG INTERACTIONS**

### **Overview**

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

### **Cytochrome P450 Inhibitors**

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

### **Transporter Protein Inhibitors**

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

### **Concomitant Therapy with Other Lipid Metabolism Regulators**

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

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



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

### **Concomitant Therapies Without Clinically Significant Interactions**

**Bile Acid Sequestrants:** Rosuvastatin calcium can be used in combination with bile acid sequestrant (e.g. cholestyramine).

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

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

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

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

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

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

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

### **Drug-Drug Interactions**

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

**Table 3 Established or Potential Drug-Drug Interactions**

<b>Proper Name</b>	<b>Effect</b>	<b>Clinical Comment</b>
Immunosuppressants (Including Cyclosporine)	Rosuvastatin calcium 10 and 20 mg were administered to cardiac transplant patients (at least 6 months post-transplant) whose	The concomitant use of rosuvastatin calcium and cyclosporine is contraindicated (see

<b>Proper Name</b>	<b>Effect</b>	<b>Clinical Comment</b>
	concomitant medication included cyclosporine, prednisone and azathioprine. Results showed that cyclosporine pharmacokinetics were not affected by rosuvastatin. However, cyclosporine did increase the systemic exposure of rosuvastatin by 11-fold ( $C_{max}$ ) and 7.1-fold ( $AUC_{[0-24]}$ ) compared with historical data in healthy individuals.	CONTRAINDICATIONS).
Protease Inhibitors	Coadministration of rosuvastatin with various protease inhibitors in combination with ritonavir to healthy volunteers resulted in the following changes to rosuvastatin plasma levels: Atazanavir 300 mg /ritonavir 100 mg (OD, 8 days), rosuvastatin calcium 10 mg (single dose); approximately a 3.1-fold increase in rosuvastatin mean $AUC_{(0-24)}$ . Lopinavir 400 mg /ritonavir 100 mg (BID, 17 days), rosuvastatin calcium 20 mg (OD, 7 days); approximately a 2.1-fold increase in rosuvastatin mean $AUC_{(0-24)}$ . 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 $AUC_{(0-24)}$ . Tipranavir 500 mg /ritonavir 200 mg (BID, 11 days), rosuvastatin calcium 10 mg (single dose); approximately a 1.4-fold increase in rosuvastatin mean $AUC_{(0-24)}$ . Fosamprenavir 700 mg /ritonavir 100 mg (OD, 8 days), rosuvastatin calcium 10 mg (single dose); no significant change in rosuvastatin mean $AUC_{(0-24)}$ .	Increased systemic exposure to rosuvastatin has been observed in subjects receiving rosuvastatin calcium with various protease inhibitors in combination with ritonavir. Consideration should be given both to the benefit of lipid lowering by the use of rosuvastatin calcium in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up-titrating rosuvastatin calcium doses in patients treated with protease inhibitors (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION, Considerations in Special Populations).
Gemfibrozil	Coadministration of a single rosuvastatin dose (10 mg) to healthy volunteers on gemfibrozil (600 mg bid) resulted in a 2.2- and 1.9-fold increase in mean $C_{max}$ and mean $AUC$ of rosuvastatin respectively.	Patients taking this combination should not exceed a dose of rosuvastatin calcium 20 mg once daily and the concomitant use of rosuvastatin calcium 40 mg once daily is contraindicated (see CONTRAINDICATIONS).
Eltrombopag	Coadministration of rosuvastatin calcium 10 mg (single dose) and eltrombopag 75 mg (OD, 10 days) to healthy volunteers resulted in approximately a 1.6-fold increase in the mean $AUC$ of rosuvastatin	The increase to rosuvastatin plasma levels should be considered when administering eltrombopag (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION, Considerations in Special Populations).
Dronedarone	Coadministration of rosuvastatin calcium and dronedarone 400 mg (bid) resulted in approximately a 1.4-fold increase in mean $AUC$ of rosuvastatin.	The increase to rosuvastatin plasma levels should be considered when administering dronedarone (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION,

<b>Proper Name</b>	<b>Effect</b>	<b>Clinical Comment</b>
		Considerations in Special Populations).
Itraconazole	Coadministration of rosuvastatin calcium 10 mg (single dose) with itraconazole 200 mg (OD, 5 days) to healthy volunteers resulted in a 1.4-fold increase in the mean AUC of rosuvastatin.	The increase to rosuvastatin plasma levels should be considered when administering itraconazole (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION, Considerations in Special Populations).
Coumarin Anticoagulants	As with other HMG-CoA reductase inhibitors, coadministration of rosuvastatin calcium and coumarin (e.g. warfarin) may result in a rise in International Normalized Ratio (INR) compared to coumarin alone. In healthy subjects, the coadministration of rosuvastatin 40 mg (10 days) and warfarin 25 mg (single dose) produced a higher mean <sub>max</sub> INR and AUC-INR than achieved with warfarin alone. Coadministration of rosuvastatin calcium 10 and 80 mg to patients on stable warfarin therapy resulted in clinically significant rises in INR (> 4, baseline 2-3). The mechanism for this effect is unknown, but is likely due to a pharmacodynamic interaction with warfarin rather than a pharmacokinetic interaction as no relevant differences in the pharmacokinetics of either drug were observed.	In patients taking coumarin monitoring of INR is recommended at initiation or cessation of therapy with rosuvastatin or following dose adjustment. Rosuvastatin therapy has not been associated with bleeding or changes in INR in patients not taking anticoagulants.
Antacids	Simultaneous dosing of rosuvastatin calcium with an antacid suspension containing aluminium and magnesium hydroxide resulted in a decrease of rosuvastatin plasma concentration by approximately 50%.	The clinical relevance of this interaction has not been studied. However, the effect was mitigated when the antacid was dosed 2 hours after rosuvastatin calcium. This interaction should not be clinically relevant in patients using this type of antacid infrequently. A frequent antacid user should be instructed to take rosuvastatin calcium at a time of day when they are less likely to need the antacid.
Oral Contraceptives	When rosuvastatin calcium 40 mg was coadministered with a representative oral contraceptive (ethinyl estradiol [35 µg] and norgestrel [180 µg on days 1 to 7, 215 µg on days 8 to 15, and 250 µg on days 16 to 21]) no reduction in contraceptive efficacy was observed. An increase in plasma concentrations (AUC) of ethinyl estradiol (26%) and norgestrel (34%) occurred.	These increased plasma levels should be considered when selecting oral contraceptive doses.

When it is necessary to coadminister rosuvastatin calcium with other medicines known to increase exposure to rosuvastatin, doses of rosuvastatin calcium should be adjusted. Start with a 5 mg once

daily dose of rosuvastatin calcium if the expected increase in exposure (AUC) is approximately 2 fold or higher. The maximum daily dose of rosuvastatin calcium should be adjusted so that the expected rosuvastatin exposure would not likely exceed that of a 40 mg daily dose of rosuvastatin calcium taken without interacting medicines, for example a 10 mg dose of rosuvastatin calcium with atazanavir/ritonavir combination (3.1 fold increase) and a 20 mg dose of rosuvastatin calcium with gemfibrozil (1.9-fold increase) (see CONTRAINDICATIONS and DRUG INTERACTIONS, Drug-Drug Interactions (Table 3)).

Drug-drug interaction studies have not been performed in pediatric patients (boys and girls who are at least one year post-menarche, 10 to 17 years of age) with heterozygous familial hypercholesterolemia.

### **Drug-Food Interactions**

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

### **Drug-Herb Interactions**

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

**Silymarin (from milk thistle):** Coadministration of silymarin (140 mg TID, 5 days) with rosuvastatin calcium (10 mg, single dose) resulted in no change in plasma concentrations of rosuvastatin.

## **DOSAGE AND ADMINISTRATION**

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

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

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

### **Recommended Dose and Dosage Adjustment**

#### **Adults**

#### **Hypercholesterolemia**

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

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

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

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

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

The dosage of NOVO-ROSUVASTATIN should be individualized according to baseline LDL-C, total C/HDL-C ratio and/or TG levels to achieve the recommended desired lipid values at the lowest possible dose.

### **Prevention of Major Cardiovascular Events**

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

### **Dosing Considerations in Special Populations**

#### **Patients with Hepatic Impairment:**

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

#### **Patients with Renal Impairment:**

The usual dose range applies in patients with mild to moderate renal impairment. Increased systemic exposure to rosuvastatin has been observed in patients with severe renal impairment. For patients with severe renal impairment (creatinine clearance < 30 mL/min/1.73 m<sup>2</sup>) the starting dose of rosuvastatin calcium should be 5 mg and not exceed 10 mg once daily (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Renal, Renal Impairment).

**Race:**

The initial dose of rosuvastatin calcium, 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 rosuvastatin calcium 20 mg once daily (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Special Populations, Race).

**Pediatrics (10 – 17 years of age):**

In pediatric patients with heterozygous familial hypercholesterolemia the recommended starting dose of CRESTOR is 5 mg taken orally once daily. The CRESTOR 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 CRESTOR doses greater than 20 mg have not been studied in this population.

Treatment experience with CRESTOR 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 WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).

**Use in Elderly:**

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

**Genetic polymorphisms:**

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

**Concomitant Therapy:**

Rosuvastatin is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when rosuvastatin calcium is administered

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

## **OVERDOSAGE**

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

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

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

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

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

### **Pharmacodynamics**

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

**See also DETAILED PHARMACOLOGY- Human Pharmacology.**

## **Pharmacokinetics**

### **Absorption:**

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

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

### **Distribution:**

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

### **Metabolism:**

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

### **Excretion:**

Following an oral dose, rosuvastatin and its metabolites are primarily excreted in the faeces (90%) with the remainder being excreted in the urine. Fecal recovery represents absorbed drug, metabolites in the bile and unabsorbed drug. The elimination half-life ( $t_{1/2}$ ) of rosuvastatin is approximately 19 hours and does not increase with increasing doses.

## **Special Populations and Conditions:**

### **Pediatrics (10 – 17 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  $C_{max}$  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.

**Race:**

A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic and Black or Afro-Caribbean groups. However, pharmacokinetic studies with rosuvastatin, including one conducted in North America, have demonstrated an approximate 2-fold elevation in median exposure ( $AUC$  and  $C_{max}$ ) in Asian subjects when compared with a Caucasian control group (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Special Populations, Race and DOSAGE AND ADMINISTRATION, Race).

**Genetic polymorphisms:**

Disposition of HMG-CoA reductase inhibitors, including rosuvastatin, involves OATP1B1 and BCRP transporter proteins. In patients with SLCO1B1 (OATP1B1) and/or ABCG2 (BCRP) genetic polymorphisms there is a risk of increased rosuvastatin exposure. Individual polymorphisms of SLCO1B1 c.521CC and ABCG2 c.421AA are associated with an approximate 1.7-fold higher rosuvastatin exposure ( $AUC$ ) or 2.4-fold higher exposure, respectively, compared to the SLCO1B1 c.521TT or ABCG2 c.421CC genotypes.

**Primary dysbetalipoproteinemia (Fredrickson Type III hyperlipoproteinemia):**

In a randomized, multicenter, double-blind crossover study, 32 patients (27 with  $\epsilon 2/\epsilon 2$  genotype and 4 with apo E mutation [Arg145Cys]) with dysbetalipoproteinemia (Fredrickson type III) received rosuvastatin calcium 10 or 20 mg daily for 6 weeks. Rosuvastatin calcium 10 and 20 mg reduced non-HDL-C (primary end point) by 48% (95% CI: 45.6, 56.7) and 56% (95% CI: 48.5, 61.4), respectively. Rosuvastatin calcium 10 and 20 mg respectively, also reduced Total-C (43% and 48%), TG (40% and 43%), VLDL-C + IDL-C (47% and 56%), LDL-C (54% and 57%), Remnant Lipoprotein Cholesterol (56% and 65%), Apo E (43% and 43%) and increased HDL-C (10% and 11%). The effect of rosuvastatin calcium on morbidity and mortality in this patient population has not been studied.

**STORAGE AND STABILITY**

Store between 15°C and 30°C.

**DOSAGE FORMS, COMPOSITION AND PACKAGING**

**Dosage Forms and Packaging**

NOVO-ROSUVASTATIN is available in tablets of 5 mg, 10 mg, 20 mg and 40 mg.

- 5 mg- Orange, round, standard convex coated tablet, debossed with “N” on one side and with “5” on the other side of the tablet. Available in bottles (100’s and 500’s) and in unit dose (30’s).
- 10 mg- Light pink to pink, round standard convex coated tablet, debossed with “N” on one side and with “10” on the other side of the tablet. Available in bottles (100’s and 500’s) and in unit dose (30’s).
- 20 mg- Light pink to pink, round standard convex coated tablet, debossed with “N” on one side and with “20” on the other side of the tablet. Available in bottles (100’s and 500’s) and in unit dose (30’s).
- 40 mg- Light pink to pink, oval shaped coated tablet, debossed with “N” on one side and with “40” on the other side of the tablet. Available in bottles (100’s and 500’s) and in unit dose (30’s).

### **Composition**

Each tablet contains 5, 10, 20 or 40 mg of rosuvastatin as rosuvastatin calcium. Each tablet also contains the following nonmedicinal ingredients: crospovidone, lactose anhydrous, microcrystalline cellulose, povidone, sodium stearyl fumarate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow, sunset yellow FCF aluminum lake (5 mg), iron oxide black (5 mg), iron oxide red (10 mg, 20 mg, 40 mg), carmoisine aluminium lake (10 mg, 20 mg, 40 mg), indigo carmine aluminium lake (10 mg, 20 mg, 40 mg).

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

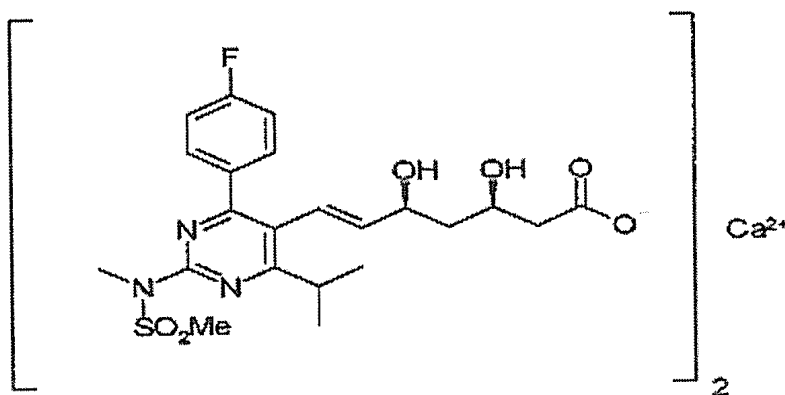
**Proper name:** rosuvastatin calcium

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

**Molecular formula**  $(C_{22}H_{27}FN_3O_6S)_2Ca$

**Molecular mass:** 1001.14 g/mol

#### Structural formula:



#### Physicochemical properties:

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

## CLINICAL TRIALS

### Comparative Bioavailability Studies

This is a blinded, single-dose, randomized, three-period, three-sequence, three-treatment, crossover study designed to evaluate the comparative bioavailability of three formulations of rosuvastatin 5 mg tablets administered to 25 healthy male subjects under fasting conditions.

Rosuvastatin (1 x 5 mg) From measured data <b>uncorrected for potency</b> Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval, 90%
AUC <sub>T</sub> (ng*h/mL)	24.621 28.336 (47)	24.130 28.134 (54)	102.03	93.65 - 111.17
AUC <sub>I</sub> (ng*h/mL)	27.908 33.615 (42)	27.802 34.293 (46)	100.38	91.25 - 110.41
C <sub>max</sub> (ng/mL)	2.909 3.329 (50)	2.989 3.432 (51)	97.34	88.07 - 107.59
T <sub>max</sub> <sup>§</sup> (h)	4.08 (20)	3.92 (24)		
T <sub>1/2</sub> <sup>§</sup> (h)	18.20 (59)	17.59 (50)		

\* Rosuvastatin 5 mg Tablets (Teva Canada Ltd.)

† Pr Crestor® 5 mg Tablets (AstraZeneca Canada Inc., Canada; purchased in Canada)

§ Expressed as the arithmetic mean (CV%)

This is a blinded, single-dose, randomized, three-period, three-sequence, three-treatment, crossover study designed to evaluate the comparative bioavailability of three formulations of rosuvastatin 40 mg tablets administered to 29 healthy male subjects under fasting conditions.

Rosuvastatin (1 x 40 mg) From measured data <b>uncorrected for potency</b> Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference 1†	% Ratio of Geometric Means	Confidence Interval, 90%
AUC <sub>T</sub> (ng*h/mL)	180.153 206.625 (55)	187.548 216.408 (51)	96.06	88.12 - 104.71
AUC <sub>I</sub> (ng*h/mL)	189.946 215.011 (55)	198.062 227.157 (50)	95.90	87.64 - 104.95
C <sub>max</sub> (ng/mL)	18.486 22.767 (72)	19.285 23.203 (61)	95.86	85.06 - 108.02
T <sub>max</sub> <sup>§</sup> (h)	3.43 (39)	3.61 (33)		
T <sub>1/2</sub> <sup>§</sup> (h)	17.94 (35)	18.84 (36)		

\* Rosuvastatin 40 mg Tablets (Teva Canada Limited)

† Pr Crestor® 40 mg Tablets (AstraZeneca Canada Inc., Canada; purchased in Canada)

§ Expressed as the arithmetic mean (CV%) only

## **Hypercholesterolemia**

### **Adults**

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

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

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

**Table 4 Dose-Response in Patients with Mild to Moderate Hypercholesterolemia (Mean Percent Change from Baseline)**

<b>ROSUVASTATIN Dose (mg/day)</b>	<b>N</b>	<b>Total-C</b>	<b>LDL-C</b>	<b>TG</b>	<b>HDL-C</b>	<b>Total-C/HDL-C</b>	<b>Apo B</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 – 17 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<sup>1</sup> received CRESTOR 5, 10 or 20 mg or placebo daily for 12 weeks and then all received CRESTOR 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  $\geq$  4.9 mmol/L or LDL-C > 4.1 mmol/L and a positive family history of premature cardiovascular disease.

CRESTOR significantly reduced LDL-C, total cholesterol and ApoB levels during the 12-week double-blind phase. Results are shown in Table 5.

**Table 5 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 (mg/day)	N	LDL-C*	HDL-C	Total-C*	TG	Non-HDL-C*	Apo B*	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
20	44	-44.6	11.2	-34.2	-13.6	-43.0	-38.1	5.4
40	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).

<sup>1</sup> 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).

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 WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).

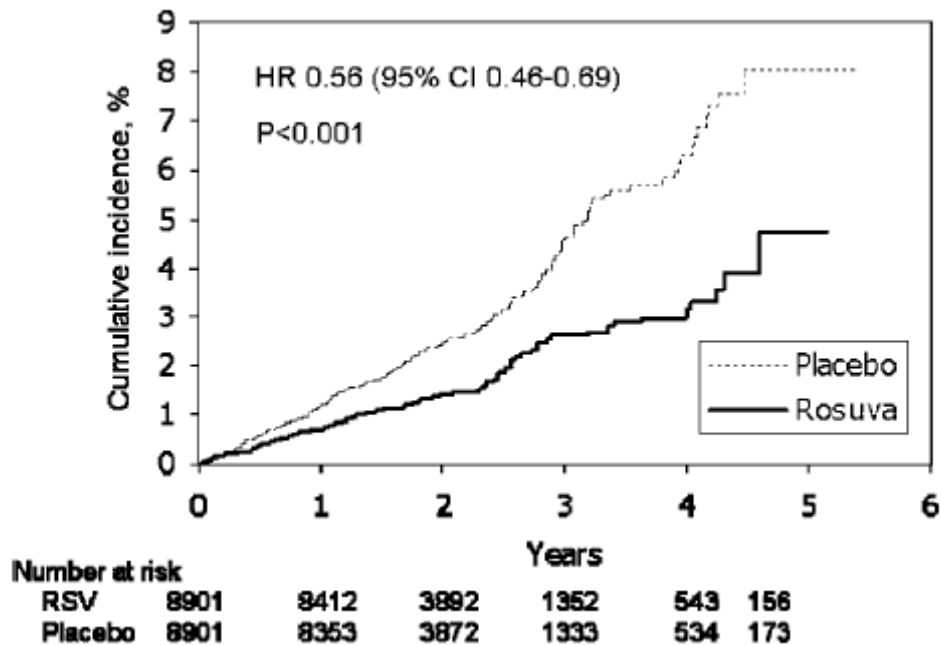
### **Prevention of Major Cardiovascular Events**

In the JUPITER study (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) 89,846 people with no pre-existing cardiovascular disease were screened and 17,802 (19.8%) were double-blindly randomized to rosuvastatin calcium 20 mg once daily (n=8901) or placebo (n=8901). Patients were followed for a median duration of 1.9 years. The main reasons for exclusion of patients were due to LDL-C  $\geq$  3.3 mmol/L (52%) or high sensitivity C-reactive protein (hsCRP) < 2 mg/L (36%). The study population consisted of 11,001 men ( $\geq$  50 years) and 6801 women ( $\geq$  60 years) without history of cardiovascular disease, LDL-C levels < 3.3 mmol/L and hsCRP levels  $\geq$  2 mg/L. Approximately 50% of the patients had an intermediate (10-20%) Framingham risk category and less than 10% were in the Framingham high (> 20%) risk category. It also included a high percentage of patients with additional risk factors such as hypertension (58%), low HDLC levels (23%), cigarette smoking (16%), a family history of premature coronary heart disease (CHD) (12%) or prediabetes (31%). Most had two (49%) or three (22%) coronary risk factors at baseline. The JUPITER study was stopped early by the Data Safety Monitoring Board due to meeting predefined stopping rules for efficacy in rosuvastatin 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 6. rosuvastatin calcium significantly reduced the risk of nonfatal myocardial infarction ( $p < 0.0001$ ), nonfatal stroke ( $p = 0.004$ ) and arterial revascularization procedures ( $p = 0.034$ ). There were no statistically significant treatment differences between the rosuvastatin calcium and placebo groups for death due to cardiovascular causes or hospitalizations for unstable angina.



**Table 6 Number of First Events by Treatment Group for the Composite Primary Endpoint (ITT population)**

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

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

£ Negative numbers imply a risk increase,

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

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

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

## DETAILED PHARMACOLOGY

### Human Pharmacology

Rosuvastatin calcium decreases elevated total cholesterol (Total-C), LDL-C, TG and increases HDL-C in patients with homozygous 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 calcium is evident within 1 week after initiation of therapy and 90% of the maximum response is usually obtained after 2 weeks. The maximum response is generally attained in 4 weeks and has been maintained in clinical trial patients followed-up for up to 1 year.

### **Animal Pharmacology**

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

Using primary preparations of hepatocytes, rosuvastatin was found to inhibit cholesterol synthesis from acetate, with an  $IC_{50}$  about 7-fold lower than the nearest comparator, atorvastatin and 40-fold lower than pravastatin. Rosuvastatin did not inhibit synthesis of cholesterol from mevalonate (the product of HMG-CoA reductase), indicating no effect on the enzymes of the sterol pathway downstream from HMG-CoA reductase. Compared to a variety of non-hepatic cells including human myoblasts, rosuvastatin was found to be highly selective for action in hepatocytes. Studies of the initial uptake rates of rosuvastatin into rat hepatocytes defined a high affinity component of uptake with a  $K_m$  of 9 mM. In addition, compared to other statins, rosuvastatin exhibited low rates of metabolism by cytochrome P450-dependent enzymes. The comparatively high potency of effect of rosuvastatin in hepatocytes may result from a combination of high affinity for the enzyme active site, active transport, and low rates of metabolism. The high degree of selectivity for action of the compound in liver cells is consistent with its octanol:water partition and with evidence of active transport into hepatocytes.

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

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

hyperlipidemic WHHL rabbit, rosuvastatin reduced Total and LDL-cholesterol and reduced the extent and degree of atherosclerotic lesions in the aorta.

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

## TOXICOLOGY

### Acute Toxicity

Rosuvastatin was shown to be of low acute toxicity following administration of single doses to rats and dogs by oral and intravenous routes. There were no mortalities in rats given an oral dose of 1000 mg/kg or 2000 mg/kg, and other than depression of bodyweight at 2000 mg/kg, there were no treatment-related effects at either dose level. Dogs received oral doses of 1000 mg/kg or 2000 mg/kg with vomiting on the day of dosing observed as the major clinical finding in both sexes. Biochemical changes (increased plasma enzymes, decreased lipids) and hematological change (increased white blood cells) were found in dogs given an oral dose of up to and including 2000 mg/kg. Lethality was observed immediately after dosing in 1/1 of rats given an intravenous dose of 500 mg/kg but two rats given 250 mg/kg intravenously showed slight hypopnea and weakness soon after dosing with no subsequent effects. The results are summarized below:

**Table 7 Acute Oral and Intravenous Toxicity Studies with Rosuvastatin**

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

### Subacute and Chronic Toxicity

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

**Table 8 Rosuvastatin: Target Organs Affected in Animal Studies**

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

\* Occurred after administration of high, intolerable doses (250 mg/kg/day [mouse gall bladder], 90 mg/kg/day [dog brain])

\*\* Unique anatomical structure not relevant to human

\*\*\* Not a consequence of prolonged dosing

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

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

Species/Finding	Margin vs. NOAEL: 40 mg			
	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)
<u>Mouse</u>				
Liver carcinoma	60	200	19	4.9
<u>Rat</u>				
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
<u>Dog</u>				
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
<u>Monkey</u>				
Testicular tubular degeneration	10	30	2.3	4
Renal tubular necrosis	10	30	2.3	4
<u>Rabbit</u>				
Muscle necrosis	1*	3*	0.2**	Not available

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

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

### Carcinogenicity/Mutagenicity

In a 104-week carcinogenicity study in rats at dose levels of 2, 20, 60 or 80 mg/kg/day, the incidence of uterine polyps was statistically significantly increased only in females at the dose of 80 mg/kg/day. This dose produced a plasma AUC<sub>(0-24)</sub> 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<sub>(0-24)</sub> 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<sub>(0-24)</sub> 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<sub>(0-24)</sub> value approximately 4.9 times higher (after correction for interspecies differences in protein binding) than the mean human plasma drug exposure after a 40 mg dose at steady state. These hepatocellular effects are known to occur in rodents treated with statins without evidence of similar effects in humans.

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

### **Teratology and Reproductive Studies**

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

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

Overall, rosuvastatin has shown no reproductive or developmental toxicity.

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19. A single dose, comparative bioavailability study between Rosuvastatin 40 mg Tablets (Teva Canada Limited) and two formulation of <sup>Pr</sup>Crestor<sup>®</sup> 40 mg Tablets (AstraZeneca Canada Inc., Canada and NV AstraZeneca SA, Belgium) in healthy subjects under fasting conditions. Data is on file at Teva Canada Limited.



## PART III CONSUMER INFORMATION

### Pr **NOVO-ROSUVASTATIN** rosuvastatin calcium tablets

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

### ABOUT THIS MEDICATION

#### What NOVO-ROSUVASTATIN is used for:

Your doctor has prescribed these pills to help lower your cholesterol or other fats in the blood (such as triglycerides) and lower the risk of heart attacks and strokes.

Rosuvastatin calcium may be prescribed in children 10 to 17 years of age with heterozygous familial hypercholesterolemia (an inherited condition causing high cholesterol levels in the blood) to lower cholesterol levels. Children require supervision from adult care givers during treatment with rosuvastatin calcium (adult care givers should read the information provided below before their child begins treatment with rosuvastatin calcium).

#### What NOVO-ROSUVASTATIN does:

Rosuvastatin Calcium belongs to the class of medications known as “statins”, more specifically called HMG-CoA reductase inhibitors. HMG-CoA reductase is an enzyme involved in regulating cholesterol levels in your body. Statins are used along with changes to diet and exercise to help control the amount of cholesterol produced by the body.

Rosuvastatin Calcium can help your body:

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

#### What is cholesterol?

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

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

There are two very different types of cholesterol.

#### *LDL cholesterol*

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

#### *HDL cholesterol*

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

#### *Important cholesterol targets*

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

#### *Lowering LDL cholesterol and Ratio*

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

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

Follow your doctor’s instructions carefully.

#### When NOVO-ROSVUASTATIN should not be used:

Do not take NOVO-ROSUVASTATIN if you:

- Currently have liver disease.
- Are pregnant or think you might be pregnant. If you become pregnant while taking NOVO-ROSUVASTATIN, discontinue use immediately and discuss with your doctor, as NOVO-ROSVUASTATIN should not be used by pregnant women.
- Are breast-feeding.
- Have ever had an allergic reaction to the active ingredient or any of the other ingredients in NOVO-ROSVUASTATIN (see **What the nonmedicinal ingredients are:**)
- Are taking a drug called cyclosporine (used, for example, after organ transplant).

#### What the medicinal ingredient is:

Rosuvastatin calcium.

#### What the nonmedicinal ingredients are:

The inactive ingredients in NOVO-ROSUVASTATIN are: Crospovidone, lactose anhydrous, microcrystalline cellulose, povidone, sodium stearyl fumarate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow, sunset yellow FCF aluminum lake (5 mg), iron oxide black (5 mg), iron oxide red (10 mg, 20 mg, 40 mg), carmoisine aluminium lake (10 mg, 20 mg, 40 mg), indigo carmine aluminium lake (10 mg, 20 mg, 40 mg)

**What dosage form it comes in:**

NOVO-ROSUVASTATIN film-coated tablets are available in 4 tablet strengths: 5 mg, 10 mg, 20 mg and 40 mg.

**WARNINGS AND PRECAUTIONS**

**Pregnancy**

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

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

Before taking your NOVO-ROSUVASTATIN tablets, tell your doctor or pharmacist if you:

- Have thyroid problems.
- Regularly drink three or more alcoholic drinks daily.
- Have a family history of muscular disorders.
- Had any past problems with your muscles (pain, tenderness), after using an HMG-CoA reductase inhibitor (statin) such as atorvastatin (LIPITOR®), fluvastatin (LESCOL®), lovastatin (MEVACOR®), pravastatin (PRAVACHOL®), rosuvastatin (CRESTOR®) or simvastatin (ZOCOR®), or have developed an allergy or intolerance to them.
- Have kidney or liver problems.
- Have diabetes.
- Have undergone surgery or other tissue injury.
- Do excessive physical exercise.

Slightly increased blood sugar can occur when you take NOVO-ROSUVASTATIN. Discuss with the doctor your risk of developing diabetes.

**INTERACTIONS WITH THIS MEDICATION:**

Sometimes drugs can interact with other drugs, so tell your doctor or pharmacist if you are taking any other medications, including prescription, non-prescription and natural health products. In particular, tell your doctor if you are taking any of the following:

- Any other cholesterol-lowering medications such as fibrates (gemfibrozil, fenofibrate), niacin or ezetimibe.
- Warfarin (or any other drug for thinning the blood).
- Ritonavir combined with another protease inhibitor (for control of HIV infection).
- Antacids (frequent use) and NOVO-ROSUVASTATIN should be taken 2 hours apart.
- Cyclosporine (used after organ transplant).

**PROPER USE OF THIS MEDICATION**

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

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

- Swallow each tablet whole with a drink of water. Take NOVO-ROSUVASTATIN as a single dose.
- Remember to take NOVO-ROSUVASTATIN at the same time every day. It does not matter if you take NOVO-ROSUVASTATIN with or without food, or in the morning or evening.
- Do not change the dose or stop taking the medicine without first talking to your doctor.
- If you get sick, have an operation, or need medical treatment while you are taking NOVO-ROSUVASTATIN, let the doctor or pharmacist know that you are taking NOVO-ROSUVASTATIN.
- If you have to see a different doctor, for any reason, be sure to tell him/her of any medicines you might be taking, including NOVO-ROSUVASTATIN.

**Usual dose:**

**Adults**

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

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

**Children 10 to 17 years of age with heterozygous familial hypercholesterolemia**

Treatment with rosuvastatin calcium is usually started at a dose of 5 mg once daily. After checking the amount of lipids in your blood, your doctor may decide to adjust your dose until you are taking the amount of rosuvastatin calcium that is right for you. The maximum daily dose is 10 mg.

**Overdose:**

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

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

**Missed dose:**

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

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

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

Check with your doctor or pharmacist promptly if any of the following persist or become troublesome:

- Stomach pain
- Headache
- Constipation
- Dizziness
- Feeling sick

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

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

Possible side effects reported with some statins: breathing problems including persistent cough and/or shortness of breath or fever; confusion, poor memory, mood problems including depression; problems sleeping including insomnia and nightmares; erectile dysfunction.

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Rare	Muscle pain that you cannot explain		√	
	Muscle tenderness or weakness, or joint pain		√	
	Breast enlargement in women and men (gynecomastia)		√	
	Generalized weakness, especially if you do not feel well		√	
	Jaundice or hepatitis symptoms like brownish or		√	

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
	discoloured urine			
	Difficulty in breathing or swallowing			√
	Allergic reaction (symptoms include swelling in the mouth, tongue, face and throat, severe itching, rash, raised lumps (hives), blistering of the skin and mucous membranes of the lips, eyes, mouth nasal passages or genitals)			√
	Liver damage: yellowing of the skin or eyes, flu-like symptoms			√
Very rare	Inflamed pancreas (pancreatitis) symptoms, such as severe stomach pain		√	
	Memory loss		√	
Unkn own	Increased blood sugar: frequent urination, thirst and hunger	√		

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

**HOW TO STORE IT**

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

### **REPORTING SUSPECTED SIDE EFFECTS**

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program  
Health Canada  
Postal Locator 0701E  
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

***NOTE: Should you require information related to the management of the side effects, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.***

### **MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals can be found by contacting Teva Canada Limited at:

1-800-268-4127 ext. 5005 (English);  
1-877-777-9117 (French)  
or [druginfo@tevacanada.com](mailto:druginfo@tevacanada.com)

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