

**CRESTOR - rosuvastatin calcium tablet, film coated
REMEDYREPACK INC.**

These highlights do not include all the information needed to use CRESTOR safely and effectively. See full prescribing information for CRESTOR. CRESTOR (rosuvastatin calcium) tablets Initial U.S. Approval: 2003

INDICATIONS & USAGE

CRESTOR is indicated as adjunctive therapy to diet to reduce elevated Total-C, LDL-C, ApoB, nonHDL-C, and triglycerides and to increase HDL-C in adult patients with primary hyperlipidemia or mixed dyslipidemia. Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and nonpharmacological interventions alone has been inadequate.

Pediatric Patients 10 to 17 years of age with Heterozygous Familial Hypercholesterolemia (HeFH)

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

CRESTOR is indicated as adjunctive therapy to diet for the treatment of adult patients with hypertriglyceridemia.

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

CRESTOR is indicated as adjunctive therapy to other lipid-lowering treatments (e.g., LDL apheresis) or alone if such treatments are unavailable to reduce LDL-C, Total-C, and ApoB in adult patients with homozygous familial hypercholesterolemia.

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

In individuals without clinically evident coronary heart disease but with an increased risk of cardiovascular disease based on age ≥ 50 years old in men and ≥ 60 years old in women, hsCRP ≥ 2 mg/L, and the presence of at least one additional cardiovascular disease risk factor such as hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease, CRESTOR is indicated to:

- reduce the risk of stroke
- reduce the risk of myocardial infarction
- reduce the risk of arterial revascularization procedures

CRESTOR has not been studied in Fredrickson Type I and V dyslipidemias.

DOSAGE & ADMINISTRATION

The dose range for CRESTOR is 5 to 40 mg orally once daily. The usual starting dose is 10-20 mg.

CRESTOR can be administered as a single dose at any time of day, with or without food.

When initiating CRESTOR therapy or switching from another HMG-CoA reductase inhibitor therapy, the appropriate CRESTOR starting dose should first be utilized, and only then titrated according to the patient's response and individualized goal of therapy.

After initiation or upon titration of CRESTOR, lipid levels should be analyzed within 2 to 4 weeks and the dosage adjusted accordingly.

The 40 mg dose of CRESTOR should be used only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose [see *Warnings and Precautions* (5.1)].

The usual dose range of CRESTOR is 5-20 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in this patient population). Doses should be individualized according to the recommended goal of therapy [see *Clinical Pharmacology* (12) and *Indications and Usage* (1.2)]. Adjustments should be made at intervals of 4 weeks or more.

The recommended starting dose of CRESTOR is 20 mg once daily. Response to therapy should be estimated from preapheresis LDL-C levels.

In Asian patients, consider initiation of CRESTOR therapy with 5 mg once daily due to increased rosuvastatin plasma concentrations. The increased systemic exposure should be taken into consideration when treating Asian patients not adequately controlled at doses up to 20 mg/day. [see *Use in Specific Populations* (8.8) and *Clinical Pharmacology* (12.3)].

Patients taking cyclosporine

The dose of CRESTOR should not exceed 5 mg once daily [see *Warnings and Precautions* (5.1) and *Drug Interactions* (7.1), and *Clinical Pharmacology* (12.3)].

Patients taking gemfibrozil

Initiate CRESTOR therapy with 5 mg once daily. The dose of CRESTOR should not exceed 10 mg once daily [see *Warnings and Precautions* (5.1) and *Drug Interactions* (7.2), and *Clinical Pharmacology* (12.3)].

Patients taking lopinavir and ritonavir or atazanavir and ritonavir

Initiate CRESTOR therapy with 5 mg once daily. The dose of CRESTOR should not exceed 10 mg once daily [see *Warnings and Precautions* (5.1) and *Drug Interactions* (7.3), and *Clinical Pharmacology* (12.3)].

For patients with severe renal impairment ($CL_{cr} < 30$ mL/min/1.73 m²) not on hemodialysis, dosing of CRESTOR should be started at 5 mg once daily and not exceed 10 mg once daily [see *Use in Specific Populations* (8.6) and *Clinical Pharmacology* (12.3)].

DOSAGE FORMS & STRENGTHS

5 mg: Yellow, round, biconvex, coated tablets. Debossed “CRESTOR” and “5” on one side of the tablet.

10 mg: Pink, round, biconvex, coated tablets. Debossed “CRESTOR” and “10” on one side of the tablet.

20 mg: Pink, round, biconvex, coated tablets. Debossed “CRESTOR” and “20” on one side of the tablet.

40 mg: Pink, oval, biconvex, coated tablets. Debossed “CRESTOR” on one side and “40” on the other side of the tablet.

CONTRAINDICATIONS

CRESTOR is contraindicated in the following conditions:

- Patients with a known hypersensitivity to any component of this product. Hypersensitivity reactions including rash, pruritus, urticaria, and angioedema have been reported with CRESTOR [see *Adverse Reactions* (6.1)].
- Patients with active liver disease, which may include unexplained persistent elevations of hepatic transaminase levels [see *Warnings and Precautions* (5.2)].
- Women who are pregnant or may become pregnant. Because HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, CRESTOR may cause fetal harm when administered to pregnant women. Additionally, there is no apparent benefit to therapy during pregnancy, and safety in pregnant women has not been established. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus and the lack of known clinical benefit with continued use during pregnancy [see *Use in Specific Populations* (8.1) and *Nonclinical Toxicology* (13.2)].
- Nursing mothers. Because another drug in this class passes into breast milk, and because HMG-CoA reductase inhibitors have the potential to cause serious adverse reactions in nursing infants, women who require CRESTOR treatment should be advised not to nurse their infants [see *Use in Specific Populations* (8.3)].

WARNINGS AND PRECAUTIONS

Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with HMG-CoA reductase inhibitors, including CRESTOR. These risks can occur at any dose level, but are increased at the highest dose (40 mg).

CRESTOR should be prescribed with caution in patients with predisposing factors for myopathy (e.g., age \geq 65 years, inadequately treated hypothyroidism, renal impairment).

The risk of myopathy during treatment with CRESTOR may be increased with concurrent administration of some other lipid-lowering therapies (fibrates or niacin), gemfibrozil, cyclosporine, lopinavir/ritonavir, or atazanavir/ritonavir [see *Dosage and Administration* (2) and *Drug Interactions* (7)].

CRESTOR therapy should be discontinued if markedly elevated creatine kinase levels occur or myopathy is diagnosed or suspected. CRESTOR therapy should also be temporarily withheld in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., sepsis, hypotension, dehydration, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, or uncontrolled seizures).

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune

myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents.

All patients should be advised promptly report to their physician unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing CRESTOR.

It is recommended that liver enzyme tests be performed before the initiation of CRESTOR, and if signs or symptoms of liver injury occur.

Increases in serum transaminases [AST (SGOT) or ALT (SGPT)] have been reported with HMG-CoA reductase inhibitors, including CRESTOR. In most cases, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy. There were two cases of jaundice, for which a relationship to CRESTOR therapy could not be determined, which resolved after discontinuation of therapy. There were no cases of liver failure or irreversible liver disease in these trials.

In a pooled analysis of placebo-controlled trials, increases in serum transaminases to >3 times the upper limit of normal occurred in 1.1% of patients taking CRESTOR versus 0.5% of patients treated with placebo.

There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including rosuvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with CRESTOR, promptly interrupt therapy. If an alternate etiology is not found, do not restart CRESTOR.

CRESTOR should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of chronic liver disease [see *Clinical Pharmacology* (12.3)]. Active liver disease, which may include unexplained persistent transaminase elevations, is a contraindication to the use of CRESTOR [see *Contraindications* (4)].

Caution should be exercised when anticoagulants are given in conjunction with CRESTOR because of its potentiation of the effect of coumarin-type anticoagulants in prolonging the prothrombin time/INR. In patients taking coumarin anticoagulants and CRESTOR concomitantly, INR should be determined before starting CRESTOR and frequently enough during early therapy to ensure that no significant alteration of INR occurs [see *Drug Interactions* (7.4)].

In the CRESTOR clinical trial program, dipstick-positive proteinuria and microscopic hematuria were observed among CRESTOR treated patients. These findings were more frequent in patients taking CRESTOR 40 mg, when compared to lower doses of CRESTOR or comparator HMG-CoA reductase inhibitors, though it was generally transient and was not associated with worsening renal function. Although the clinical significance of this finding is unknown, a dose reduction should be considered for patients on CRESTOR therapy with unexplained persistent proteinuria and/or hematuria during routine urinalysis testing.

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including CRESTOR [see *Adverse Reactions* (6.1)].

Although clinical studies have shown that CRESTOR alone does not reduce basal plasma cortisol concentration or impair adrenal reserve, caution should be exercised if CRESTOR is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones such

as ketoconazole, spironolactone, and cimetidine.

ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:
•Rhabdomyolysis with myoglobinuria and acute renal failure and myopathy (including myositis) [see *Warnings and Precautions* (5.1)]•Liver enzyme abnormalities [see *Warnings and Precautions* (5.2)]

In the CRESTOR controlled clinical trials database (placebo or active-controlled) of 5394 patients with a mean treatment duration of 15 weeks, 1.4% of patients discontinued due to adverse reactions. The most common adverse reactions that led to treatment discontinuation were:

•Myalgia•abdominal pain•nausea

The most commonly reported adverse reactions (incidence $\geq 2\%$) in the CRESTOR controlled clinical trial database of 5394 patients were:

•headache •myalgia •abdominal pain •asthenia•nausea

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

Adverse reactions reported in $\geq 2\%$ of patients in placebo-controlled clinical studies and at a rate greater than placebo are shown in Table 1. These studies had a treatment duration of up to 12 weeks.

Table 1. Adverse Reactions* Reported by $\geq 2\%$ of Patients Treated with CRESTOR and > Placebo in Placebo-Controlled Trials (% of Patients)

Adverse Reactions	CRESTOR 5 mg N=291	CRESTOR 10 mg N=283	CRESTOR 20 mg N=64	CRESTOR 40 mg N=106	Total CRESTOR 5 mg – 40 mg N=744	Placebo N=382
Headache	5.5	4.9	3.1	8.5	5.5	5.0
Nausea	3.8	3.5	6.3	0	3.4	3.1
Myalgia	3.1	2.1	6.3	1.9	2.8	1.3
Asthenia	2.4	3.2	4.7	0.9	2.7	2.6
Constipation	2.1	2.1	4.7	2.8	2.4	2.4

Other adverse reactions reported in clinical studies were abdominal pain, dizziness, hypersensitivity (including rash, pruritus, urticaria, and angioedema) and pancreatitis. The following laboratory abnormalities have also been reported: dipstick-positive proteinuria and microscopic hematuria [see *Warnings and Precautions* (5.4)]; elevated creatine phosphokinase, transaminases, glucose, glutamyl transpeptidase, alkaline phosphatase, and bilirubin; and thyroid function abnormalities.

In the METEOR study, involving 981 participants treated with rosuvastatin 40 mg (n=700) or placebo (n=281) with a mean treatment duration of 1.7 years, 5.6% of subjects treated with CRESTOR versus 2.8% of placebo-treated subjects discontinued due to adverse reactions. The most common adverse reactions that led to treatment discontinuation were: myalgia, hepatic enzyme increased, headache, and nausea [see *Clinical Studies* (14.7)].

Adverse reactions reported in $\geq 2\%$ of patients and at a rate greater than placebo are shown in Table 2.

Table 2. Adverse Reactions* Reported by ≥ 2% of Patients Treated with CRESTOR and > Placebo in the METEOR Trial (% of Patients)

Adverse Reactions	CRESTOR 40 mg N=700	Placebo N=281
Myalgia	12.7	12.1
Arthralgia	10.1	7.1
Headache	6.4	5.3
Dizziness	4.0	2.8
Increased CPK	2.6	0.7
Abdominal pain	2.4	1.8
†ALT >3x ULN	2.2	0.7

In the JUPITER study, 17,802 participants were treated with rosuvastatin 20 mg (n=8901) or placebo (n=8901) for a mean duration of 2 years. A higher percentage of rosuvastatin-treated patients versus placebo-treated patients, 6.6% and 6.2%, respectively, discontinued study medication due to an adverse event, irrespective of treatment causality. Myalgia was the most common adverse reaction that led to treatment discontinuation.

In JUPITER, there was a significantly higher frequency of diabetes mellitus reported in patients taking rosuvastatin (2.8%) versus patients taking placebo (2.3%). Mean HbA1c was significantly increased by 0.1% in rosuvastatin-treated patients compared to placebo-treated patients. The number of patients with a HbA1c > 6.5% at the end of the trial was significantly higher in rosuvastatin-treated versus placebo-treated patients [see *Warnings and Precautions* (5.5) and *Clinical Studies* (14.8)].

Adverse reactions reported in ≥ 2% of patients and at a rate greater than placebo are shown in Table 3.

Table 3. Adverse Reactions* Reported by ≥ 2% of Patients Treated with CRESTOR and > Placebo in the JUPITER Trial (% of Patients)

Adverse Reactions	CRESTOR 20 mg N=8901	Placebo N=8901
Myalgia	7.6	6.6
Arthralgia	3.8	3.2
Constipation	3.3	3.0
Nausea	2.4	2.3

In a 12-week controlled study in boys and postmenarchal girls, the safety and tolerability profile of CRESTOR 5 to 20 mg daily was generally similar to that of placebo [see *Clinical Studies* (14.6) and *Use in Specific Populations, Pediatric Use* (8.4)].

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

The following adverse reactions have been identified during postapproval use of CRESTOR: arthralgia, fatal and non-fatal hepatic failure, hepatitis, jaundice, depression, sleep disorders (including insomnia and nightmares) and gynecomastia. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a

causal relationship to drug exposure.

There have been rare reports of immune-mediated necrotizing myopathy associated with statin use [see *Warnings and Precautions* (5.1)].

There have been rare postmarketing 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 nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

¹ Adverse reactions by COSTART preferred term.

² Adverse reactions by MedDRA preferred term.

³ Frequency recorded as abnormal laboratory value.

⁴ Treatment-emergent adverse reactions by MedDRA preferred term.

DRUG INTERACTIONS

Cyclosporine increased rosuvastatin exposure (AUC) 7-fold. Therefore, in patients taking cyclosporine, the dose of CRESTOR should not exceed 5 mg once daily [see *Dosage and Administration* (2.5), *Warnings and Precautions* (5.1), and *Clinical Pharmacology* (12.3)].

Gemfibrozil significantly increased rosuvastatin exposure. Due to an observed increased risk of myopathy/rhabdomyolysis, combination therapy with CRESTOR and gemfibrozil should be avoided. If used together, the dose of CRESTOR should not exceed 10 mg once daily [see *Clinical Pharmacology* (12.3)].

Coadministration of rosuvastatin with certain protease inhibitors given in combination with ritonavir has differing effects on rosuvastatin exposure. The protease inhibitor combinations lopinavir/ritonavir and atazanavir/ritonavir increase rosuvastatin exposure (AUC) up to threefold [see *Table 4 – Clinical Pharmacology* (12.3)]. For these combinations the dose of CRESTOR should not exceed 10 mg once daily. The combinations of tipranavir/ritonavir or fosamprenavir/ritonavir produce little or no change in rosuvastatin exposure. Caution should be exercised when rosuvastatin is coadministered with protease inhibitors given in combination with ritonavir [see *Dosage and Administration* (2.5), *Warnings and Precautions* (5.1) and *Clinical Pharmacology* (12.3)].

CRESTOR significantly increased INR in patients receiving coumarin anticoagulants. Therefore, caution should be exercised when coumarin anticoagulants are given in conjunction with CRESTOR. In patients taking coumarin anticoagulants and CRESTOR concomitantly, INR should be determined before starting CRESTOR and frequently enough during early therapy to ensure that no significant alteration of INR occurs [see *Warnings and Precautions* (5.3) and *Clinical Pharmacology* (12.3)].

The risk of skeletal muscle effects may be enhanced when CRESTOR is used in combination with lipid-modifying doses (≥ 1 g/day) of niacin; caution should be used when prescribing with CRESTOR [see *Warnings and Precautions* (5.1)].

When CRESTOR was coadministered with fenofibrate, no clinically significant increase in the AUC of rosuvastatin or fenofibrate was observed. Because it is known that the risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concomitant use of fenofibrates, caution should be used when prescribing fenofibrates with CRESTOR [see *Warnings and Precautions* (5.1) and *Clinical Pharmacology* (12.3)].

USE IN SPECIFIC POPULATIONS

CRESTOR is contraindicated in women who are or may become pregnant. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol products are essential for fetal development. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hyperlipidemia therapy [see *Contraindications* (4)].

There are no adequate and well-controlled studies of CRESTOR in pregnant women. There have been rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors. In a review of about 100 prospectively followed pregnancies in women exposed to other HMG-CoA reductase inhibitors, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed the rate expected in the general population. However, this study was only able to exclude a three-to-fourfold increased risk of congenital anomalies over background incidence. In 89% of these cases, drug treatment started before pregnancy and stopped during the first trimester when pregnancy was identified.

Rosuvastatin crosses the placenta in rats and rabbits. In rats, CRESTOR was not teratogenic at systemic exposures equivalent to a human therapeutic dose of 40 mg/day. At 10-12 times the human dose of 40 mg/day, there was decreased pup survival, decreased fetal body weight among female pups, and delayed ossification. In rabbits, pup viability decreased and maternal mortality increased at doses equivalent to the human dose of 40 mg/day [see *Nonclinical Toxicology* (13.2)].

CRESTOR may cause fetal harm when administered to a pregnant woman. If the patient becomes pregnant while taking CRESTOR, the patient should be apprised of the potential risks to the fetus and the lack of known clinical benefit with continued use during pregnancy.

It is not known whether rosuvastatin is excreted in human milk, but a small amount of another drug in this class does pass into breast milk. In rats, breast milk concentrations of rosuvastatin are three times higher than plasma levels; however, animal breast milk drug levels may not accurately reflect human breast milk levels. Because another drug in this class passes into human milk and because HMG-CoA reductase inhibitors have a potential to cause serious adverse reactions in nursing infants, women who require CRESTOR treatment should be advised not to nurse their infants [see *Contraindications* (4)].

The safety and effectiveness of CRESTOR in patients 10 to 17 years of age with heterozygous familial hypercholesterolemia were evaluated in a controlled clinical trial of 12 weeks duration followed by 40 weeks of open-label exposure. Patients treated with 5 mg, 10 mg, and 20 mg daily CRESTOR had an adverse experience profile generally similar to that of patients treated with placebo [see *Adverse Reactions* (6.2)]. Although not all adverse reactions identified in the adult population have been observed in clinical trials of children and adolescent patients, the same warnings and precautions for adults should be considered for children and adolescents. There was no detectable effect of CRESTOR on growth, weight, BMI (body mass index), or sexual maturation [see *Clinical Studies* (14.5)] in pediatric patients (10 to 17 years of age). Adolescent females should be counseled on appropriate contraceptive methods while on CRESTOR therapy [see *Use in Specific Populations* (8.1)]. CRESTOR has not been

studied in controlled clinical trials involving prepubertal patients or patients younger than 10 years of age. Doses of CRESTOR greater than 20 mg have not been studied in the pediatric population.

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

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

Of the 10,275 patients in clinical studies with CRESTOR, 3159 (31%) were 65 years and older, and 698 (6.8%) were 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Elderly patients are at higher risk of myopathy and CRESTOR should be prescribed with caution in the elderly [see *Warnings and Precautions* (5.1) and *Clinical Pharmacology* (12.3)].

Rosuvastatin exposure is not influenced by mild to moderate renal impairment ($CL_{cr} \geq 30$ mL/min/1.73 m²); however, exposure to rosuvastatin is increased to a clinically significant extent in patients with severe renal impairment who are not receiving hemodialysis. CRESTOR dosing should be adjusted in patients with severe renal impairment ($CL_{cr} < 30$ mL/min/1.73 m²) not requiring hemodialysis [see *Dosage and Administration* (2.6), *Warnings and Precautions* (5.1) and *Clinical Pharmacology* (12.3)].

CRESTOR is contraindicated in patients with active liver disease, which may include unexplained persistent elevations of hepatic transaminase levels. Chronic alcohol liver disease is known to increase rosuvastatin exposure; CRESTOR should be used with caution in these patients [see *Contraindications* (4), *Warning and Precautions* (5.2), and *Clinical Pharmacology* (12.3)].

Pharmacokinetic studies have demonstrated an approximate 2-fold increase in median exposure to rosuvastatin in Asian subjects when compared with Caucasian controls. CRESTOR dosage should be adjusted in Asian patients [see *Dosage and Administration* (2.4) and *Clinical Pharmacology* (12.3)].

OVERDOSAGE

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

DESCRIPTION

CRESTOR (rosuvastatin calcium) is a synthetic lipid-lowering agent for oral administration.

The chemical name for rosuvastatin calcium is 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

with the following structural formula:

The empirical formula for rosuvastatin calcium is $(C_{22}H_{27}FN_3O_6S)_2Ca$ and the molecular weight is 1001.14. Rosuvastatin calcium is a white amorphous powder that is sparingly soluble in water and methanol, and slightly soluble in ethanol. Rosuvastatin calcium is a hydrophilic compound with a partition coefficient (octanol/water) of 0.13 at pH of 7.0.

CRESTOR Tablets for oral administration contain 5, 10, 20, or 40 mg of rosuvastatin and the following inactive ingredients: Each tablet contains: microcrystalline cellulose NF, lactose monohydrate NF, tribasic calcium phosphate NF, crospovidone NF, magnesium stearate NF, hypromellose NF, triacetin NF, titanium dioxide USP, yellow ferric oxide, and red ferric oxide NF.

CLINICAL PHARMACOLOGY

CRESTOR is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. *In vivo* studies in animals, and *in vitro* studies in cultured animal and human cells have shown rosuvastatin to have a high uptake into, and selectivity for, action in the liver, the target organ for cholesterol lowering. In *in vivo* and *in vitro* studies, rosuvastatin produces its lipid-modifying effects in two ways. First, it increases the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL. Second, rosuvastatin inhibits hepatic synthesis of VLDL, which reduces the total number of VLDL and LDL particles.

•**Absorption:** In clinical pharmacology studies in man, peak plasma concentrations of rosuvastatin were reached 3 to 5 hours following oral dosing. Both C_{max} and AUC increased in approximate proportion to CRESTOR dose. The absolute bioavailability of rosuvastatin is approximately 20%. Administration of CRESTOR with food did not affect the AUC of rosuvastatin. The AUC of rosuvastatin does not differ following evening or morning drug administration. •**Distribution:** Mean volume of distribution at steady-state of rosuvastatin is approximately 134 liters. Rosuvastatin is 88% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentrations. •**Metabolism:** Rosuvastatin is not extensively metabolized; approximately 10% of a radiolabeled dose is recovered as metabolite. The major metabolite is N-desmethyl rosuvastatin, which is formed principally by cytochrome P450 2C9, and *in vitro* studies have demonstrated that N-desmethyl rosuvastatin has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of the parent compound. Overall, greater than 90% of active plasma HMG-CoA reductase inhibitory activity is accounted for by the parent compound. •**Excretion:** Following oral administration, rosuvastatin and its metabolites are primarily

excreted in the feces (90%). The elimination half-life ($t_{1/2}$) of rosuvastatin is approximately 19 hours. After an intravenous dose, approximately 28% of total body clearance was via the renal route, and 72% by the hepatic route. •**Race:** A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic, and Black or Afro-Caribbean groups. However, pharmacokinetic studies, including one conducted in the US, have demonstrated an approximate 2-fold elevation in median exposure (AUC and C_{max}) in Asian subjects when compared with a Caucasian control group. •**Gender:** There were no differences in plasma concentrations of rosuvastatin between men and women. •**Geriatric:** There were no differences in plasma concentrations of rosuvastatin between the nonelderly and elderly populations (age ≥ 65 years). •**Renal Impairment:** Mild to moderate renal impairment ($CL_{cr} \geq 30$ mL/min/1.73 m²) had no influence on plasma concentrations of rosuvastatin. However, plasma concentrations of rosuvastatin increased to a clinically significant extent (about 3-fold) in patients with severe renal impairment ($CL_{cr} < 30$ mL/min/1.73 m²) not receiving hemodialysis compared with healthy subjects ($CL_{cr} > 80$ mL/min/1.73 m²). •**Hemodialysis:** Steady-state plasma concentrations of rosuvastatin in patients on chronic hemodialysis were approximately 50% greater compared with healthy volunteer subjects with normal renal function. •**Hepatic Impairment:** In patients with chronic alcohol liver disease, plasma concentrations of rosuvastatin were modestly increased. •In patients with Child-Pugh A disease, C_{max} and AUC were increased by 60% and 5%, respectively, as compared with patients with normal liver function. In patients with Child-Pugh B disease, C_{max} and AUC were increased 100% and 21%, respectively, compared with patients with normal liver function.

Drug-Drug Interactions:

Rosuvastatin clearance is not dependent on metabolism by cytochrome P450 3A4 to a clinically significant extent.

Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter organic anion-transporting polyprotein 1B1 (OATP1B1) and efflux transporter breast cancer resistance protein (BCRP). Concomitant administration of CRESTOR with medications that are inhibitors of these transporter proteins (e.g. cyclosporine, certain HIV protease inhibitors) may result in increased rosuvastatin plasma concentrations and an increased risk of myopathy [see *Dosage and Administration* (2.5)].

Coadministered drug and dosing regimen	Rosuvastatin		
	Dose (mg)*	Change in AUC†	Change in C_{max}‡
Cyclosporine – stable dose required (75 mg – 200 mg BID)	10 mg QD for 10 days	↑ 7.1-fold†	↑ 11-fold†
Atazanavir/ritonavir combination 300 mg/100 mg QD for 8 days	10 mg	↑ 3.1-fold†	↑ 7-fold†
Lopinavir/ritonavir combination 400 mg/100 mg BID for 17 days	20 mg QD for 7 days	↑ 2.1-fold†	↑ 5-fold†
Gemfibrozil 600 mg BID for 7 days	80 mg	↑ 1.9-fold†	↑ 2.2-fold†
Eltrombopag 75 mg QD, 5 days	10 mg	↑ 1.6-fold	↑ 2-fold
Darunavir 600 mg/ritonavir 100 mg BID, 7 days	10 mg QD for 7 days	↑ 1.5-fold	↑ 2.4-fold
Tipranavir/ritonavir combination 500 mg/200mg BID for 11 days	10 mg	↑ 26%	↑ 2.2-fold
Dronedaron 400 mg BID	10 mg	↑ 1.4-fold	
Itraconazole 200 mg QD, 5 days	10 mg or 80 mg	↑ 39% ↑ 28%	↑ 36% ↑ 15%
Ezetimibe 10 mg QD, 14 days	10 mg QD for 14 days	↑ 1.2-fold	

Fosamprenavir/ritonavir 700 mg/100 mg BID for 7 days	10 mg	↑ 8%	↑ 45%
Fenofibrate 67 mg TID for 7 days	10 mg	↔	↑21%
Rifampicin 450 mg QD, 7 days	20 mg	↔	
Aluminum & magnesium hydroxide combination antacid	40 mg	↓ 54% [†]	↓ 50% [†]
Administered simultaneously	40 mg	↓ 22%	↓ 16%
Administered 2 hours apart			
Ketoconazole 200 mg BID for 7 days	80 mg	↑ 2%	↓ 5%
Fluconazole 200 mg QD for 11 days	80 mg	↑ 14%	↑ 9%
Erythromycin 500 mg QID for 7 days	80 mg	↓ 20%	↓ 31%

Table 5. Effect of Rosuvastatin Coadministration on Systemic Exposure To Other Drugs

Rosuvastatin Dosage Regimen		Coadministered Drug		
		Name and Dose	Change in AUC	Change in C _{max}
40 mg QD for 10 days	Warfarin* 25 mg single dose		R- Warfarin ↑ 4%	R- Warfarin ↓ 1%
			S-Warfarin ↑ 6%	S-Warfarin 0%
40 mg QD for 12 days	Digoxin 0.5 mg single dose		↑ 4%	↑ 4%
40 mg QD for 28 days	Oral Contraceptive (ethinyl estradiol 0.035 mg & norgestrel 0.180, 0.215 and 0.250 mg) QD for 21 Days		EE ↑ 26% NG ↑ 34%	EE ↑ 25% NG ↑ 23%

EE = ethinyl estradiol,
NG = norgestrel

⁵ Single dose unless otherwise noted.

⁶ Mean ratio (with/without coadministered drug and no change = 1-fold) or % change (with/without coadministered drug and no change = 0%); symbols of ↑ and ↓ indicate the exposure increase and decrease, respectively.

⁷ Clinically significant [

⁸ Clinically significant pharmacodynamic effects [

NONCLINICAL TOXICOLOGY

In a 104-week carcinogenicity study in rats at dose levels of 2, 20, 60, or 80 mg/kg/day by oral gavage, the incidence of uterine stromal polyps was significantly increased in females at 80 mg/kg/day at systemic exposure 20 times the human exposure at 40 mg/day based on AUC. Increased incidence of polyps was not seen at lower doses.

In a 107-week carcinogenicity study in mice given 10, 60, 200 mg/kg/day by oral gavage, an increased incidence of hepatocellular adenoma/carcinoma was observed at 200 mg/kg/day at systemic exposures 20 times the human exposure at 40 mg/day based on AUC. An increased incidence of hepatocellular tumors was not seen at lower doses.

Rosuvastatin was not mutagenic or clastogenic with or without metabolic activation in the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the mouse lymphoma assay, and the chromosomal aberration assay in Chinese hamster lung cells. Rosuvastatin was negative in the *in vivo* mouse micronucleus test.

In rat fertility studies with oral gavage doses of 5, 15, 50 mg/kg/day, males were treated for 9 weeks prior to and throughout mating and females were treated 2 weeks prior to mating and throughout mating until gestation day 7. No adverse effect on fertility was observed at 50 mg/kg/day (systemic exposures up to 10 times the human exposure at 40 mg/day based on AUC). In testicles of dogs treated with rosuvastatin at 30 mg/kg/day for one month, spermatidic giant cells were seen. Spermatidic giant cells were observed in monkeys after 6-month treatment at 30 mg/kg/day in addition to vacuolation of seminiferous tubular epithelium. Exposures in the dog were 20 times and in the monkey 10 times the human exposure at 40 mg/day based on body surface area. Similar findings have been seen with other drugs in this class.

Embryo-fetal Development

Rosuvastatin crosses the placenta and is found in fetal tissue and amniotic fluid at 3% and 20%, respectively, of the maternal plasma concentration following a single 25 mg/kg oral gavage dose on gestation day 16 in rats. A higher fetal tissue distribution (25% maternal plasma concentration) was observed in rabbits after a single oral gavage dose of 1 mg/kg on gestation day 18.

In female rats given oral gavage doses of 5, 15, 50 mg/kg/day rosuvastatin before mating and continuing through day 7 postcoitus results in decreased fetal body weight (female pups) and delayed ossification at the high dose (systemic exposures 10 times the human exposure at 40 mg/day based on AUC).

In pregnant rats given oral gavage doses of 2, 10, 50 mg/kg/day from gestation day 7 through lactation day 21 (weaning), decreased pup survival occurred in groups given 50 mg/kg/day, systemic exposures \geq 12 times the human exposure at 40 mg/day based on body surface area.

In pregnant rabbits given oral gavage doses of 0.3, 1, 3 mg/kg/day from gestation day 6 to lactation day 18 (weaning), exposures equivalent to the human exposure at 40 mg/day based on body surface area, decreased fetal viability and maternal mortality was observed.

Rosuvastatin was not teratogenic in rats at \leq 25 mg/kg/day or in rabbits \leq 3 mg/kg/day (systemic exposures equivalent to the human exposure at 40 mg/day based on AUC or body surface area, respectively).

Central Nervous System Toxicity

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with several other members of this drug class. A chemically similar drug in this class produced dose-dependent optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in dogs, at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose. Edema, hemorrhage, and partial necrosis in the interstitium of the choroid plexus was observed in a female dog sacrificed moribund at day 24 at 90 mg/kg/day by oral gavage (systemic exposures 100 times the human exposure at 40 mg/day based on AUC). Corneal opacity was seen in dogs treated for 52 weeks at 6 mg/kg/day by oral gavage (systemic exposures 20 times the human exposure at 40 mg/day based on AUC). Cataracts were seen in dogs treated for 12 weeks by oral gavage at 30 mg/kg/day (systemic exposures 60 times the human exposure at 40 mg/day based on AUC). Retinal dysplasia and retinal loss were seen in dogs treated for 4 weeks by oral gavage at 90 mg/kg/day

(systemic exposures 100 times the human exposure at 40 mg/day based on AUC). Doses ≤ 30 mg/kg/day (systemic exposures ≤ 60 times the human exposure at 40 mg/day based on AUC) did not reveal retinal findings during treatment for up to one year.

CLINICAL STUDIES

CRESTOR reduces Total-C, LDL-C, ApoB, nonHDL-C, and TG, and increases HDL-C, in adult patients with hyperlipidemia and mixed dyslipidemia.

Dose-Ranging Study: In a multicenter, double-blind, placebo-controlled, dose-ranging study in patients with hyperlipidemia CRESTOR given as a single daily dose for 6 weeks significantly reduced Total-C, LDL-C, nonHDL-C, and ApoB, across the dose range (Table 6).

Table 6. Dose-Response in Patients With Hyperlipidemia (Adjusted Mean % Change From Baseline at Week 6)

Dose	N	Total-C	LDL-C	Non-HDL-C	ApoB	TG	HDL-C
Placebo	13	-5	-7	-7	-3	-3	3
CRESTOR 5 mg	17	-33	-45	-44	-38	-35	13
CRESTOR 10 mg	17	-36	-52	-48	-42	-10	14
CRESTOR 20 mg	17	-40	-55	-51	-46	-23	8
CRESTOR 40 mg	18	-46	-63	-60	-54	-28	10

Active-Controlled Study: CRESTOR was compared with the HMG-CoA reductase inhibitors atorvastatin, simvastatin, and pravastatin in a multicenter, open-label, dose-ranging study of 2240 patients with hyperlipidemia or mixed dyslipidemia. After randomization, patients were treated for 6 weeks with a single daily dose of either CRESTOR, atorvastatin, simvastatin, or pravastatin (Figure 1 and Table 7).

Figure 1. Percent LDL-C Change by Dose of CRESTOR, Atorvastatin, Simvastatin, and Pravastatin at Week 6 in Patients with Hyperlipidemia or Mixed Dyslipidemia

Box plots are a representation of the 25th, 50th, and 75th percentile values, with whiskers representing the 10th and 90th percentile values. Mean baseline LDL-C: 189 mg/dL

Table 7. Percent Change in LDL-C From Baseline to Week 6 (LS Mean*) by Treatment Group (sample sizes ranging from 156–167 patients per group)

Treatment	Treatment Daily Dose			
	10 mg	20 mg	40 mg	80 mg
CRESTOR	-46†	-52‡	-55§	---
Atorvastatin	-37	-43	-48	-51
Simvastatin	-28	-35	-39	-46
Pravastatin	-20	-24	-30	---

Active-Controlled Study: In a study of patients with heterozygous FH (baseline mean LDL of 291), patients were randomized to CRESTOR 20 mg or atorvastatin 20 mg. The dose was increased by 6-week intervals. Significant LDL-C reductions from baseline were seen at each dose in both treatment groups (Table 8).

Table 8. Mean LDL-C Percentage Change from Baseline

		CRESTOR (n=435) LS Mean * (95% CI)	Atorvastatin (n=187) LS Mean ¹³ (95% CI)
Week 6	20mg	-47% (-49%, -46%)	-38% (-40%, -36%)
Week 12	40mg	-55% (-57%, -54%)	-47% (-49%, -45%)
Week 18	80mg	NA	-52% (-54%, -50%)

Dose-Response Study: In a double-blind, placebo-controlled dose-response study in patients with baseline TG levels from 273 to 817 mg/dL, CRESTOR given as a single daily dose (5 to 40 mg) over 6 weeks significantly reduced serum TG levels (Table 9).

Table 9. Dose-Response in Patients With Primary Hypertriglyceridemia Over 6 Weeks Dosing Median (Min, Max) Percent Change From Baseline

Dose	Placebo (n=26)	CRESTOR 5 mg (n=25)	CRESTOR 10 mg (n=23)	CRESTOR 20 mg (n=27)	CRESTOR 40 mg (n=25)
Triglycerides	1 (-40, 72)	-21 (-58, 38)	-37 (-65, 5)	-37 (-72, 11)	-43 (-80, -7)
nonHDL-C	2 (-13, 19)	-29 (-43, -8)	-49 (-59, -20)	-43 (-74, 12)	-51 (-62, -6)
VLDL-C	2 (-36, 53)	-25 (-62, 49)	-48 (-72, 14)	-49 (-83, 20)	-56 (-83, 10)
Total-C	1 (-13, 17)	-24 (-40, -4)	-40 (-51, -14)	-34 (-61, -11)	-40 (-51, -4)
LDL-C	5 (-30, 52)	-28 (-71, 2)	-45 (-59, 7)	-31 (-66, 34)	-43 (-61, -3)
HDL-C	-3 (-25, 18)	3 (-38, 33)	8 (-8, 24)	22 (-5, 50)	17 (-14, 63)

In a randomized, multicenter, double-blind crossover study, 32 patients (27 with $\epsilon 2/\epsilon 2$ and 4 with apo E mutation [Arg145Cys] with primary dysbetalipoproteinemia (Type III Hyperlipoproteinemia) entered a 6-week dietary lead-in period on the NCEP Therapeutic Lifestyle Change (TLC) diet. Following dietary lead-in, patients were randomized to a sequence of treatments in conjunction with the TLC diet for 6 weeks each: rosuvastatin 10 mg followed by rosuvastatin 20 mg or rosuvastatin 20 mg followed

by rosuvastatin 10 mg. CRESTOR reduced nonHDL-C (primary end point) and circulating remnant lipoprotein levels. Results are shown in the table below.

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

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

Dose-Titration Study: In an open-label, forced-titration study, homozygous FH patients (n=40, 8-63 years) were evaluated for their response to CRESTOR 20 to 40 mg titrated at a 6-week interval. In the overall population, the mean LDL-C reduction from baseline was 22%. About one-third of the patients benefited from increasing their dose from 20 mg to 40 mg with further LDL lowering of greater than 6%. In the 27 patients with at least a 15% reduction in LDL-C, the mean LDL-C reduction was 30% (median 28% reduction). Among 13 patients with an LDL-C reduction of <15%, 3 had no change or an increase in LDL-C. Reductions in LDL-C of 15% or greater were observed in 3 of 5 patients with known receptor negative status.

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

Rosuvastatin significantly reduced LDL-C (primary end point), total cholesterol and ApoB levels at each dose compared to placebo. Results are shown in Table 11 below.

Table 11 – Lipid-modifying effects of rosuvastatin in pediatric patients 10 to 17 years of age

with heterozygous familial hypercholesterolemia (least-squares mean percent change from baseline to week 12)

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

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

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

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

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

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

In the **Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER)** study, the effect of CRESTOR (rosuvastatin calcium) on the occurrence of major cardiovascular (CV) disease events was assessed in 17,802 men (≥50 years) and women (≥60 years) who had no clinically evident cardiovascular disease, LDL-C levels <130 mg/dL (3.3 mmol/l) and hs-CRP levels ≥2 mg/L. The study population had an estimated baseline coronary heart disease risk of 11.6% over 10 years based on the Framingham risk criteria and included a high percentage of patients with additional risk factors such as hypertension (58%), low HDL-C levels (23%), cigarette smoking (16%), or a family history of premature CHD (12%). Study participants had a median baseline LDL-C of 108 mg/dL and hsCRP of 4.3 mg/L. Study participants were randomly assigned to placebo (n=8901) or rosuvastatin 20 mg once daily (n=8901) and were followed for a mean duration of 2 years. The JUPITER study was stopped early by the Data Safety Monitoring Board due to meeting predefined stopping rules for efficacy in rosuvastatin-treated subjects.

The primary end point was a composite end point consisting of the time-to-first occurrence of any of the following major CV events: CV death, nonfatal myocardial infarction, nonfatal stroke, hospitalization

for unstable angina or an arterial revascularization procedure.

Rosuvastatin significantly reduced the risk of major CV events (252 events in the placebo group vs. 142 events in the rosuvastatin group) with a statistically significant ($p < 0.001$) relative risk reduction of 44% and absolute risk reduction of 1.2% (see Figure 2). The risk reduction for the primary end point was consistent across the following predefined subgroups: age, sex, race, smoking status, family history of premature CHD, body mass index, LDL-C, HDL-C, and hsCRP levels.

Figure 2. Time to first occurrence of major cardiovascular events in JUPITER

The individual components of the primary end point are presented in Figure 3. Rosuvastatin significantly reduced the risk of nonfatal myocardial infarction, nonfatal stroke, and arterial revascularization procedures. There were no significant treatment differences between the rosuvastatin and placebo groups for death due to cardiovascular causes or hospitalizations for unstable angina.

Rosuvastatin significantly reduced the risk of myocardial infarction (6 fatal events and 62 nonfatal events in placebo-treated subjects vs. 9 fatal events and 22 nonfatal events in rosuvastatin-treated subjects) and the risk of stroke (6 fatal events and 58 nonfatal events in placebo-treated subjects vs. 3 fatal events and 30 nonfatal events in rosuvastatin-treated subjects).

In a post-hoc subgroup analysis of JUPITER subjects ($n=1405$; rosuvastatin=725, placebo=680) with a hsCRP ≥ 2 mg/L and no other traditional risk factors (smoking, BP $\geq 140/90$ or taking antihypertensives, low HDL-C) other than age, after adjustment for high HDL-C, there was no significant treatment benefit with rosuvastatin treatment.

Figure 3. Major CV events by treatment group in JUPITER

At one year, rosuvastatin increased HDL-C and reduced LDL-C, hsCRP, total cholesterol and serum triglyceride levels ($p < 0.001$ for all versus placebo).

⁹ Corresponding standard errors are approximately 1.00

¹⁰CRESTOR 10 mg reduced LDL-C significantly more than atorvastatin 10 mg; pravastatin 10 mg, 20 mg, and 40 mg; simvastatin 10 mg, 20 mg, and 40 mg. ($p < 0.002$)

¹¹CRESTOR 20 mg reduced LDL-C significantly more than atorvastatin 20 mg and 40 mg; pravastatin 20 mg and 40 mg; simvastatin 20 mg, 40 mg, and 80 mg. ($p < 0.002$)

¹²CRESTOR 40 mg reduced LDL-C significantly more than atorvastatin 40 mg; pravastatin 40 mg; simvastatin 40 mg, and 80 mg. ($p < 0.002$)

¹³LS Means are least square means adjusted for baseline LDL-C

¹⁴Median percent change

¹⁵Difference from placebo not statistically significant

HOW SUPPLIED

CRESTOR[®] (rosuvastatin calcium) Tablets are supplied as:

•NDC 0310-0755-90: 5 mg. Yellow, round, biconvex, coated tablets. Debossed “CRESTOR” and “5” on one side; bottle of 90 tablets
•NDC 0310-0751-90: 10 mg. Pink, round, biconvex, coated tablets. Debossed “CRESTOR” and “10” on one side; bottle of 90 tablets
•NDC 0310-0751-39: 10 mg. Pink, round, biconvex, coated tablets. Debossed “CRESTOR” and “10” on one side; unit dose packages of 100
•NDC 0310-0752-90: 20 mg. Pink, round, biconvex, coated tablets. Debossed “CRESTOR” and “20” on one side; bottles of 90
•NDC 0310-0752-39: 20 mg. Pink, round, biconvex, coated tablets. Debossed “CRESTOR” and “20” on one side; unit dose packages of 100
•NDC 0310-0754-30: 40 mg. Pink, oval, biconvex, coated tablets. Debossed “CRESTOR” on one side and “40” on the other side; bottles of 30

Storage

Store at controlled room temperature, 20-25°C (68-77°F) [see USP Controlled Room Temperature]. Protect from moisture.

INFORMATION FOR PATIENTS

Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever or if these muscle signs or symptoms persist after discontinuing CRESTOR.

When taking CRESTOR with an aluminum and magnesium hydroxide combination antacid, the antacid should be taken at least 2 hours after CRESTOR administration.

If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus and the lack of known clinical benefit with continued use during pregnancy.

It is recommended that liver enzyme tests be performed before the initiation of CRESTOR and if signs or symptoms of liver injury occur. All patients treated with CRESTOR should be advised to promptly report any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice.

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ASTRAZENECA

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PATIENT INFORMATION

CRESTOR[®] (rosuvastatin calcium) Tablets

(Kres-tor)

Read this information carefully before you start taking CRESTOR. Each time you refill your prescription for CRESTOR, read the patient information, as there may be new information. This summary does not include everything there is to know about CRESTOR and does not take the place of talking with your health care professional about your medical condition or treatment.

If you have any questions about CRESTOR, ask your health care professional. Only your health care professional can tell you if CRESTOR is right for you.

What is CRESTOR?

CRESTOR is a prescription medicine that belongs to a group of cholesterol-lowering medicines called statins. Along with diet, CRESTOR lowers “bad” cholesterol (LDL-C), increases “good” cholesterol (HDL-C). If bad cholesterol levels are left untreated, fatty deposits (plaque) can build up in the walls of the blood vessels. This plaque buildup over time, can lead to narrowing of these vessels. This is one of the most common causes of heart disease. By lowering bad cholesterol in your blood, CRESTOR can slow this plaque buildup in the walls of blood vessels. CRESTOR has been proven to reduce the risk of heart attacks and strokes in older adults without known heart disease.

What is Cholesterol?

Cholesterol is a fatty substance, also called a lipid, normally found in your bloodstream. Your body

needs a certain amount of cholesterol to function properly. But high cholesterol can lead to health problems. LDL-C is called bad cholesterol because if you have too much in your bloodstream, it can become a danger to your health and can lead to potentially serious conditions. HDL-C is known as good cholesterol because it may help remove excess cholesterol.

Common health factors such as diabetes, high blood pressure, smoking, obesity, family history of early heart disease, and age can make controlling your cholesterol even more important.

What is Atherosclerosis?

Atherosclerosis is the progressive buildup of plaque in the arteries over time. One major cause is high levels of LDL-C. Other health factors, such as family history, diabetes, high blood pressure, or if you smoke, or are overweight, may also play a role in the formation of plaque in arteries. Often this plaque starts building up in arteries in early adulthood and gets worse over time.

How Does CRESTOR Work?

Most of the cholesterol in your blood is made in the liver. CRESTOR works by reducing cholesterol in two ways: CRESTOR blocks an enzyme in the liver causing the liver to make less cholesterol, and CRESTOR increases the uptake and breakdown by the liver of cholesterol already in the blood.

Who Should Not Take CRESTOR?

Do not take CRESTOR if you:

- are pregnant or think you may be pregnant, or are planning to become pregnant. CRESTOR may harm your unborn baby. If you become pregnant, stop taking CRESTOR and call your health care professional right away
- are breast-feeding. CRESTOR can pass into your breast milk and may harm your baby
- have liver problems
- have had an allergic reaction to CRESTOR or are allergic to any of its ingredients. The active ingredient is rosuvastatin calcium. The inactive ingredients are: microcrystalline cellulose, lactose monohydrate, tribasic calcium phosphate, crospovidone, magnesium stearate, hypromellose, triacetin, titanium dioxide, yellow ferric oxide, and red ferric oxide

The safety and effectiveness of CRESTOR have not been established in pediatric patients under the age of 10.

What should I tell my health care professional before taking CRESTOR?

Tell your health care professional if you:

- have a history of muscle pain or weakness
- are pregnant or think you may be pregnant, or are planning to become pregnant
- are breast-feeding
- drink more than 2 glasses of alcohol daily
- have liver problems
- have kidney problems
- have thyroid problems
- are Asian or of Asian descent

Tell your health care professional about all medicines you take or plan to take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may interact with CRESTOR, causing side effects. It is particularly important to tell your health care professional if you are taking or plan to take medicines for:

- your immune system
- cholesterol/triglycerides
- blood thinning
- HIV/AIDS
- preventing pregnancy

Know all of the medicines you take and what they look like. It's always a good idea to check that you have the right prescription before you leave the pharmacy and before you take any medicine. Keep a list of your medicines with you to show your health care professional.

If you need to go to the hospital or have surgery, tell all of your health care professionals about all medicines that you are taking.

How Should I Take CRESTOR?

Take CRESTOR exactly as prescribed by your health care professional. Do not change your dose or stop CRESTOR without talking to your health care professional, even if you are feeling well.

Your health care professional may do blood tests to check your cholesterol levels before and during your treatment with CRESTOR. Your dose of CRESTOR may be changed based on these blood test results.

CRESTOR can be taken at any time of day, with or without food.

Swallow the tablets whole.

Your health care professional may start you on a cholesterol lowering diet before giving you CRESTOR. Stay on this diet when you take CRESTOR.

Wait at least 2 hours after taking CRESTOR to take an antacid that contains a combination of aluminum and magnesium hydroxide.

If you miss a dose of CRESTOR, take it as soon as you remember. However, **do not take 2 doses of CRESTOR within 12 hours of each other.**

If you take too much CRESTOR or overdose, call your health care professional or a Poison Control Center right away or go to the nearest emergency room.

What Should I Avoid While Taking CRESTOR?

Talk to your health care professional before you start any new medicines. This includes prescription and nonprescription medicines, vitamins, and herbal supplements. CRESTOR and certain other medicines can interact, causing serious side effects.

Talk to your health care professional if you are pregnant or plan to become pregnant. Do not use CRESTOR if you are pregnant, trying to become pregnant or suspect that you are pregnant. If you become pregnant while taking CRESTOR, stop taking it and contact your health care professional immediately.

What are the Possible Side Effects of CRESTOR?

CRESTOR can cause side effects in some people.

Serious side effects may include:

Muscle Problems. Call your health care professional right away if you experience unexplained muscle pain, tenderness, or weakness especially with fever. This may be an early sign of a rare muscle problem that could lead to serious kidney problems. The risk of muscle problems is greater in people who are 65 years of age or older, or who already have thyroid or kidney problems. The chance of muscle problems may be increased if you are taking certain other medicines with CRESTOR.

If you have muscle problems that do not go away even after your health care professional has advised you to stop taking CRESTOR, notify your health care professional. Your health care professional may do further tests to diagnose the cause of your muscle problems.

Liver problems. Your health care professional should do blood tests to check your liver before you start taking CRESTOR and if you have symptoms of liver problems while you take CRESTOR. Call your doctor right away if you have any of the following symptoms of liver problems:

- feel unusually tired or weak
- loss of appetite
- upper belly pain
- dark urine
- yellowing of your skin or the whites of your eyes

The most common side effects may include:

Headache, muscle aches and pains, abdominal pain, weakness, and nausea.

The following additional side effects have been reported with CRESTOR:

Memory loss and confusion

This is not a complete list of side effects of CRESTOR. Talk to your health care professional for a complete list or if you have side effects that bother you or that do not go away.

How Do I Store CRESTOR?

Store CRESTOR at room temperature, 68 to 77°F (20 to 25°C) and in a dry place.

If your health care professional tells you to stop treatment or if your medicine is out of date, throw the medicine away.

Keep CRESTOR and all medicines in a secure place and out of the reach of children.

What are the Ingredients in CRESTOR?

Active Ingredient: rosuvastatin as rosuvastatin calcium

Inactive Ingredients: microcrystalline cellulose NF, lactose monohydrate NF, tribasic calcium phosphate NF, crospovidone NF, magnesium stearate NF, hypromellose NF, triacetin NF, titanium dioxide USP, yellow ferric oxide, and red ferric oxide NF.

General Information About CRESTOR

It is important to take CRESTOR as prescribed and to discuss any health changes you experience while taking CRESTOR with your health care professional. Do not use CRESTOR for a condition for which it was not prescribed. Do not give CRESTOR to other people, even if they have the same medical condition you have. It may harm them.

This leaflet summarizes important information about CRESTOR. If you would like more information about CRESTOR, ask your health care professional. You can also go to the CRESTOR website at www.crestor.com or call 1-800-CRESTOR.

CRESTOR is a trademark of the AstraZeneca group of companies.

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Distributed by:

AstraZeneca Pharmaceuticals LP

Wilmington, DE 19850

ASTRAZENECA

Rev. December 2012

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL SECTION

DRUG: CRESTOR

GENERIC: Rosuvastatin calcium

DOSAGE: TABLET, FILM COATED

ADMINISTRATION: ORAL

NDC: 52125-033-02

STRENGTH: 5 mg

COLOR: yellow

SHAPE: ROUND

SCORE: No score

SIZE: 7 mm

IMPRINT: 30

QTY: 30



CRESTOR

5 MG TAB
QTY:00030

NDC#: 52125-0033-02 INT:MS ID#:5

EXPIRES: 07/2013

LOT#: DP712012345

COL: yellow

SHP: round

DIST: ASTRAZENECA PHARMA WILMINGTON DE 19850

MFG: IPR PHARMA INC CANOVANAS PR 00729

A. Caution Federal law prohibits transfer of this drug to any person other than for whom it was prescribed.

B. Store at a temperature between 15 degree C and 30 degree C (59 degree F and 86 degree F) (see USP)

C. Re-packaged by: RemydRapack Inc. 656 Koller Dr., Indiana, PA 15701. 1-724-466-8762





PHARMACY SERVICES

START

		16	8
	23	15	7
	22		6
	21		5
	20	13	4
	19	11	3
26	18	10	2
25	17	9	1
24			

CRESTOR

rosuvastatin calcium tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:52125-033(NDC:0310-0755)
Route of Administration	ORAL	DEA Schedule	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ROSUVASTATIN CALCIUM (UNII: 83MVU38M7Q) (ROSUVASTATIN - UNII:413KH5ZJ73)	ROSUVASTATIN	5 mg

Inactive Ingredients

Ingredient Name	Strength
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
TRIACETIN (UNII: XHX3C3X673)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
TRIBASIC CALCIUM PHOSPHATE (UNII: 91D9GV0Z28)	
CROSPVIDONE (UNII: 68401960MK)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	

Product Characteristics

Color	yellow	Score	no score
Shape	ROUND (TABLET, FILM COATED)	Size	7mm
Flavor		Imprint Code	5;crestor
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:52125-033-02	30 in 1 BLISTER PACK		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021366	02/27/2013	

Labeler - REMEDYREPACK INC. (829572556)

