FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CRESTOR is indicated:

- To reduce the risk of stroke, myocardial infarction, and arterial revascularization procedures in adults without established coronary heart disease who are at increased risk of cardiovascular (CV) disease based on age, hsCRP ≥2 mg/L, and at least one additional CV risk factor.
- As an adjunct to diet to:
    - Reduce LDL-C in adults with primary hyperlipidemia.
    - Reduce low-density lipoprotein cholesterol (LDL-C) and slow the progression of atherosclerosis in adults.
    - Reduce LDL-C in adults and pediatric patients aged 8 years and older with heterozygous familial hypercholesterolemia (HeFH).
- As an adjunct to other LDL-C-lowering therapies, or alone if such treatments are unavailable, to reduce LDL-C in adults and pediatric patients aged 7 years and older with homozygous familial hypercholesterolemia (HoFH).
- As an adjunct to diet for the treatment of adults with:
    - Primary dysbetalipoproteinemia.
    - Hypertriglyceridemia.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosage and Administration Information

- Administer CRESTOR orally as a single dose at any time of day, with or without food. The tablet should be swallowed whole.
- Assess LDL-C when clinically appropriate, as early as 4 weeks after initiating CRESTOR, and adjust the dosage if necessary.
- If a dose is missed, advise patients not take an extra dose. Resume treatment with the next dose.

2.2 Recommended Dosage in Adult Patients

- The dosage range for CRESTOR is 5 to 40 mg orally once daily.
- The recommended dose of CRESTOR depends on a patient's indication for usage, LDL-C, and individual risk for cardiovascular events.

5 WARNINGS AND PRECAUTIONS

5.1 Myopathy and Rhabdomyolysis

CRESTOR may cause myopathy [muscle pain, tenderness, or weakness associated with elevated creatine kinase (CK)] and rhabdomyolysis. Acute kidney injury secondary to myoglobinuria and rare fatalities have occurred as a result of rhabdomyolysis with statins, including CRESTOR.

Risk Factors for Myopathy

Risk factors for myopathy include age 65 years or greater, uncontrolled hypothyroidism, renal impairment, concomitant use with certain other drugs (including other lipid-lowering therapies), and higher CRESTOR dosage. Asian patients on CRESTOR may be at higher risk for myopathy *[see Drug Interactions (7.1) and Use in Specific Populations (8.8)]*. The myopathy risk is greater in patients taking CRESTOR 40 mg daily compared with lower CRESTOR dosages.

Steps to Prevent or Reduce the Risk of Myopathy and Rhabdomyolysis

The concomitant use of CRESTOR with cyclosporine or gemfibrozil is not recommended. CRESTOR dosage modifications are recommended for patients taking certain antiviral medications, darolutamide, and regorafenib *[see Dosage and Administration (2.6)]*. Niacin, fibrates, and colchicine may also increase the risk of myopathy and rhabdomyolysis *[see Drug Interactions (7.1)]*.

Discontinue CRESTOR if markedly elevated CK levels occur or if myopathy is either diagnosed or suspected. Muscle symptoms and CK elevations may resolve if CRESTOR is discontinued. Temporarily discontinue CRESTOR in patients experiencing an acute or serious condition at high risk of developing renal failure secondary to rhabdomyolysis (e.g., sepsis; shock; severe hypovolemia; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy).

Inform patients of the risk of myopathy and rhabdomyolysis when starting or increasing the CRESTOR dosage. Instruct patients to promptly report any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

5.2 Immune-Mediated Necrotizing Myopathy

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use, including reports of recurrence when the same or a different statin was administered. IMNM is characterized by proximal muscle weakness and elevated serum creatine kinase that persist despite discontinuation of statin treatment; positive anti-HMG CoA reductase antibody; muscle biopsy showing necrotizing myopathy; and improvement with immunosuppressive agents. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required. Discontinue CRESTOR if IMNM is suspected.

In the JUPITER study, patients were treated with CRESTOR 20 mg (n=8901) or placebo (n=8901) for a mean duration of 2 years. In JUPITER, there was a significantly higher frequency of diabetes mellitus reported in patients taking CRESTOR (2.8%) versus patients taking placebo (2.3%). Mean HbA1c was significantly increased by 0.1% in CRESTOR-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 CRESTOR-treated versus placebo-treated patients *[see Clinical Studies (14)]*.

Adverse reactions reported in ≥2% of patients and at a rate greater than placebo are shown in Table 4.

Table 4: Adverse Reactions Reported in ≥2% of Patients Treated with CRESTOR and > Placebo in the JUPITER Trial

Adverse Reactions	Placebo N=8901 %	CRESTOR 20 mg N=8901 %
Myalgia	6.6	7.6
Arthralgia	3.2	3.8
Constipation	3.0	3.3
Diabetes mellitus	2.3	2.8
Nausea	2.3	2.4

Pediatric Patients with HeFH

In a 12-week controlled study in pediatric patients 10 to 17 years of age with HeFH with CRESTOR 5 to 20 mg daily *[see Use in Specific Populations (8.4) and Clinical Studies (14)]*, elevations in serum CK greater than 10 x ULN were observed more frequently in CRESTOR-treated patients compared with patients receiving placebo. Four of 130 (3%) patients treated with CRESTOR (2 treated with 10 mg and 2 treated with 20 mg) had increased CK greater than 10 x ULN, compared to 0 of 46 patients on placebo.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of CRESTOR. 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.

Blood Disorders: thrombocytopenia

Hepatobiliary Disorders: hepatitis, jaundice, fatal and non-fatal hepatic failure

Musculoskeletal Disorders: arthralgia, rare reports of immune-mediated necrotizing myopathy associated with statin use

Nervous System Disorders: peripheral neuropathy, rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, and confusion)

associated with the use of 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). There have been rare reports of new-onset or exacerbation of myasthenia gravis, including ocular myasthenia, and reports of recurrence when the same or a different statin was administered.

Psychiatric Disorders: depression, sleep disorders (including insomnia and nightmares)

Reproductive System and Breast Disorders: gynecomastia

Respiratory Disorders: interstitial lung disease

Skin and Subcutaneous Tissue Disorders: drug reaction with eosinophilia and systemic symptoms (DRESS), lichenoid drug eruption

7 DRUG INTERACTIONS

7.1 Drug Interactions that Increase the Risk of Myopathy and Rhabdomyolysis with CRESTOR

Rosuvastatin is a substrate of CYP2C9 and transporters (such as OATP1B1, BCRP). Rosuvastatin plasma levels can be significantly increased with concomitant administration of inhibitors of CYP2C9 and transporters. Table 5 includes a list of drugs that increase the risk of myopathy and rhabdomyolysis when used concomitantly with CRESTOR and instructions for preventing or managing them *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

Table 5: Drug Interactions that Increase the Risk of Myopathy and Rhabdomyolysis with CRESTOR

Cyclosporine	
Clinical Impact:	Cyclosporine increased rosuvastatin exposure 7-fold. The risk of myopathy and rhabdomyolysis is increased with concomitant use of cyclosporine or gemfibrozil with CRESTOR.
Intervention:	If used concomitantly, do not exceed a dose of CRESTOR 5 mg once daily.
Teriflunomide	
Clinical Impact:	Teriflunomide increased rosuvastatin exposure more than 2.5-fold. The risk of myopathy and rhabdomyolysis is increased with concomitant use.
Intervention:	In patients taking teriflunomide, do not exceed a dose of CRESTOR 10 mg once daily.
Enasidenib	
Clinical Impact:	Enasidenib increased rosuvastatin exposure more than 2.4-fold. The risk of myopathy and rhabdomyolysis is increased with concomitant use.
Intervention:	In patients taking enasidenib, do not exceed a dose of CRESTOR 10 mg once daily.
Capmatinib	

Clinical Impact:	Capmatinib increased rosuvastatin exposure more than 2.1-fold. The risk of myopathy and rhabdomyolysis is increased with concomitant use.	
Intervention:	In patients taking capmatinib, do not exceed a dose of CRESTOR 10 mg once daily.	
Fostamatinib		
Clinical Impact:	Fostamatinib increased rosuvastatin exposure more than 2.0-fold. The risk of myopathy and rhabdomyolysis is increased with concomitant use.	
Intervention:	In patients taking fostamatinib, do not exceed a dose of CRESTOR 20 mg once daily.	
Febuxostat		
Clinical Impact:	Febuxostat increased rosuvastatin exposure more than 1.9-fold. The risk of myopathy and rhabdomyolysis is increased with concomitant use.	
Intervention:	In patients taking febuxostat, do not exceed a dose of CRESTOR 20 mg once daily.	
Gemfibrozil		
Clinical Impact:	Gemfibrozil significantly increased rosuvastatin exposure and gemfibrozil may cause myopathy when given alone. The risk of myopathy and rhabdomyolysis is increased with concomitant use of gemfibrozil with CRESTOR.	
Intervention:	Avoid concomitant use of gemfibrozil with CRESTOR. If used concomitantly, initiate CRESTOR at 5 mg once daily and do not exceed a dose of CRESTOR 10 mg once daily.	
Tafamidis		
Clinical Impact:	Tafamidis significantly increased rosuvastatin exposure and tafamidis may cause myopathy when given alone. The risk of myopathy and rhabdomyolysis is increased with concomitant use of tafamidis with CRESTOR.	
Intervention:	Avoid concomitant use of tafamidis with CRESTOR. If used concomitantly, initiate CRESTOR at 5 mg once daily and do not exceed a dose of CRESTOR 20 mg once daily. Monitor for signs of myopathy and rhabdomyolysis if used concomitantly with CRESTOR.	
Anti-Viral Medications		
Clinical Impact:	Rosuvastatin plasma levels were significantly increased with concomitant administration of many anti-viral drugs, which increases the risk of myopathy and rhabdomyolysis.	
Intervention:	• Sofosbuvir/velpatasvir/voxilaprevir • Ledipasvir/sofosbuvir	Avoid concomitant use with CRESTOR.
	• Simeprevir • Dasabuvir/ombitasvir/paritaprevir/ritonavir • Elbasvir/grazoprevir	Initiate with CRESTOR 5 mg once daily, and

7.2 Drug Interactions that Decrease the Efficacy of CRESTOR

Table 6 presents drug interactions that may decrease the efficacy of CRESTOR and instructions for preventing or managing them.

Table 6: Drug Interactions that Decrease the Efficacy of CRESTOR

Antacids	
Clinical Impact:	Concomitant aluminum and magnesium hydroxide combination antacid administration decreased the mean exposure of rosuvastatin 50% *[see Clinical Pharmacology (12.3)]*.
Intervention:	In patients taking antacid, administer CRESTOR at least 2 hours after the antacid .

7.3 CRESTOR Effects on Other Drugs

Table 7 presents CRESTOR's effect on other drugs and instructions for preventing or managing them.

Table 7: CRESTOR Effects on Other Drugs

Warfarin	
Clinical Impact:	Rosuvastatin significantly increased the INR in patients receiving warfarin *[see Clinical Pharmacology (12.3)]*.
Intervention:	In patients taking warfarin, obtain an INR before starting CRESTOR and frequently enough after initiation, dose titration or discontinuation to ensure that no significant alteration in INR occurs. Once the INR is stable, monitor INR at regularly recommended intervals.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Discontinue CRESTOR when pregnancy is recognized. Alternatively, consider the ongoing therapeutic needs of the individual patient.

CRESTOR decreases synthesis of cholesterol and possibly other biologically active substances derived from cholesterol; therefore, CRESTOR may cause fetal harm when administered to pregnant patients based on the mechanism of action *[see Clinical Pharmacology (12.1)]*. In addition, treatment of hyperlipidemia is not generally necessary during pregnancy. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hyperlipidemia for most patients.

Available data from case series and prospective and retrospective observational cohort studies over decades of use with statins in pregnant women have not identified a drug-associated risk of major congenital malformations. Published data from prospective and retrospective observational

Advanced age (≥65 years) is a risk factor for CRESTOR-associated myopathy and rhabdomyolysis. Dose selection for an elderly patient should be cautious, recognizing the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of myopathy. Monitor geriatric patients receiving CRESTOR for the increased risk of myopathy *[see Warnings and Precautions (5.1)]*.

8.6 Renal Impairment

Rosuvastatin exposure is not influenced by mild to moderate renal impairment (CL_{cr} ≥30 mL/min/1.73 m^2). Exposure to rosuvastatin is increased to a clinically significant extent in patients with severe renal impairment (CL_{cr} <30 mL/min/1.73 m^2) who are not receiving hemodialysis *[see Clinical Pharmacology (12.3)]*.

Renal impairment is a risk factor for myopathy and rhabdomyolysis. Monitor all patients with renal impairment for development of myopathy. In patients with severe renal impairment not on hemodialysis, the recommended starting dosage is 5 mg daily and should not exceed 10 mg daily *[see Dosage and Administration (2.5) and Warnings and Precautions (5.1)]*.

8.7 Hepatic Impairment

CRESTOR is contraindicated in patients with acute liver failure or decompensated cirrhosis. Chronic alcohol liver disease is known to increase rosuvastatin exposure. Patients who consume substantial quantities of alcohol and/or have a history of liver disease may be at increased risk for hepatic injury *[see Contraindications (4), Warning and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

8.8 Asian Patients

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

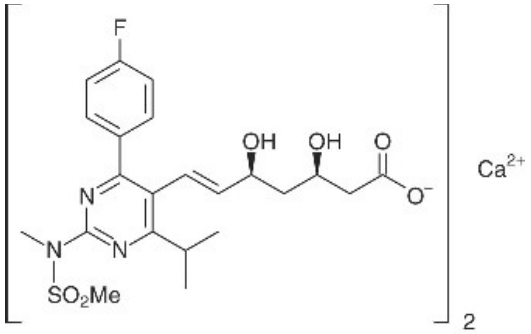
10 OVERDOSAGE

No specific antidotes for CRESTOR are known. Hemodialysis does not significantly enhance clearance of rosuvastatin. Contact Poison Control (1-800-222-1222) for latest recommendations.

11 DESCRIPTION

CRESTOR (rosuvastatin) is a 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA)-reductase inhibitor.

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 use contain rosuvastatin 5 mg, 10 mg, 20 mg, or 40 mg (equivalent to 5.2 mg, 10.4 mg, 20.8 mg, and 41.6 mg rosuvastatin calcium) and the following inactive ingredients: crospovidone NF, hypromellose NF, lactose monohydrate NF, magnesium stearate NF, microcrystalline cellulose NF, red ferric oxide NF, titanium dioxide USP, triacetin NF, tribasic calcium phosphate NF and yellow ferric oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CRESTOR is an inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol.

12.2 Pharmacodynamics

Inhibition of HMG-CoA reductase by rosuvastatin accelerates the expression of LDL-receptors, followed by the uptake of LDL-C from blood to the liver, leading to a decrease in plasma LDL-C and total cholesterol. Sustained inhibition of cholesterol synthesis in the liver also decreases levels of very-low-density lipoproteins. The maximum LDL-C reduction of CRESTOR is usually achieved by 4 weeks and is maintained after that.

12.3 Pharmacokinetics

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

Table 8: Effect of Coadministered Drugs on Rosuvastatin Systemic Exposure

Coadministered drug and dosing regimen	**Rosuvastatin**		
		Mean Ratio (ratio with/without coadministered drug) No Effect=1.0	
	Dose (mg)[1]	**Change in AUC**	**Change in C_{max}**
Febuxostat 120 mg QD for 4 days	10 mg, single dose	1.9[2] (1.5-2.5)[3]	2.1[2] (1.8-2.6)[3]
Gemfibrozil 600 mg BID for 7 days	80 mg	1.9[2] (1.6-2.2)[3]	2.2[2] (1.8-2.7)[3]
Tafamidis 61 mg BID on Days 1 & 2, followed by QD on Days 3 to 9	10 mg	1.97[2] (1.68-2.31)[3]	1.86[2] (1.59-2.16)[3]
Eltrombopag 75 mg QD, 5 days	10 mg	1.6 (1.4-1.7)[3]	2 (1.8-2.3)[3]
Darunavir 600 mg/ritonavir 100 mg BID, 7 days	10 mg, QD for 7 days	1.5 (1.0-2.1)[3]	2.4 (1.6-3.6)[3]
Tipranavir/ritonavir combination 500 mg/200 mg BID for 11 days	10 mg	1.4 (1.2-1.6)[3]	2.2 (1.8-2.7)[3]
Dronedarone 400 mg BID	10 mg	1.4	
Itraconazole 200 mg QD, 5 days	10 mg or 80 mg	1.4 (1.2-1.6)[3] 1.3 (1.1-1.4)[3]	1.4 (1.2-1.5)[3] 1.2 (0.9-1.4)[3]
Ezetimibe 10 mg QD, 14 days	10 mg, QD for 14 days	1.2 (0.9-1.6)[3]	1.2 (0.8-1.6)[3]
Fosamprenavir/ritonavir 700 mg/100 mg BID for 7 days	10 mg	1.1	1.5
Fenofibrate 67 mg TID for 7 days	10 mg	↔	1.2 (1.1-1.3)[3]
Rifampicin 450 mg QD, 7 days	20 mg	↔	
Aluminum & magnesium hydroxide combination antacid Administered simultaneously Administered 2 hours apart	 40 mg 40 mg	 0.5[2] (0.4-0.5)[3] 0.8 (0.7-0.9)[3]	 0.5[2] (0.4-0.6)[3] 0.8 (0.7-1.0)[3]
Ketoconazole 200 mg BID for 7 days	80 mg	1.0 (0.8-1.2)[3]	1.0 (0.7-1.3)[3]
Fluconazole 200 mg QD for 11 days	80 mg	1.1 (1.0-1.3)[3]	1.1 (0.9-1.4)[3]
Erythromycin 500 mg QID for 7 days	80 mg	0.8	0.7

Table 8: Effect of Coadministered Drugs on Rosuvastatin Systemic Exposure

Coadministered drug and dosing regimen	**Rosuvastatin**		
		Mean Ratio (ratio with/without coadministered drug) No Effect=1.0	
	Dose (mg)[1]	**Change in AUC**	**Change in C_{max}**
		(0.7-0.9)[3]	(0.5-0.9)[3]

QD= Once daily, BID= Twice daily, TID= Three times daily, QID= Four times daily

[1] Single dose unless otherwise noted.

[2] Clinically significant *[see Dosage and Administration (2) and Warnings and Precautions (5)]*

[3] Mean ratio with 90% CI (with/without coadministered drug, e.g., 1= no change, 0.7 = 30% decrease, 11=11-fold increase in exposure)

Table 9: Effect of Rosuvastatin Coadministration on Systemic Exposure to Other Drugs

Rosuvastatin Dosage Regimen	**Coadministered Drug**		
		Mean Ratio (ratio with/without coadministered drug) No Effect=1.0	
	Name and Dose	**Change in AUC**	**Change in C_{max}**
40 mg QD for 10 days	Warfarin[1] 25 mg single dose	R- Warfarin 1.0 (1.0-1.1)[2] S-Warfarin 1.1 (1.0-1.1)[2]	R-Warfarin 1.0 (0.9-1.0)[2] S-Warfarin 1.0 (0.9-1.1)[2]
40 mg QD for 12 days	Digoxin 0.5 mg single dose	1.0 (0.9-1.2)[2]	1.0 (0.9-1.2)[2]
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 1.3 (1.2-1.3)[2] NG 1.3 (1.3-1.4)[2]	EE 1.3 (1.2-1.3)[2] NG 1.2 (1.1-1.3)[2]

EE = ethinyl estradiol, NG = norgestrel, QD= Once daily

[1] Clinically significant pharmacodynamic effects *[see Drug Interactions (7.3)]*

[2] Mean ratio with 90% CI (with/without coadministered drug, e.g., 1= no change, 0.7=30% decrease, 11=11-fold increase in exposure)

12.5 Pharmacogenomics

Disposition of rosuvastatin, involves OATP1B1 and other transporter proteins. Higher plasma concentrations of rosuvastatin have been reported in very small groups of patients (n=3 to 5) who have two reduced function alleles of the gene that encodes OATP1B1 (*SLCO1B1* 521T > C). The frequency of this genotype (i.e., *SLCO1B1* 521 C/C) is generally lower than 5% in most racial/ethnic groups. The impact of this polymorphism on efficacy and/or safety of CRESTOR has not been clearly established.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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, or 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.

14 CLINICAL STUDIES

Primary Prevention of Cardiovascular Disease

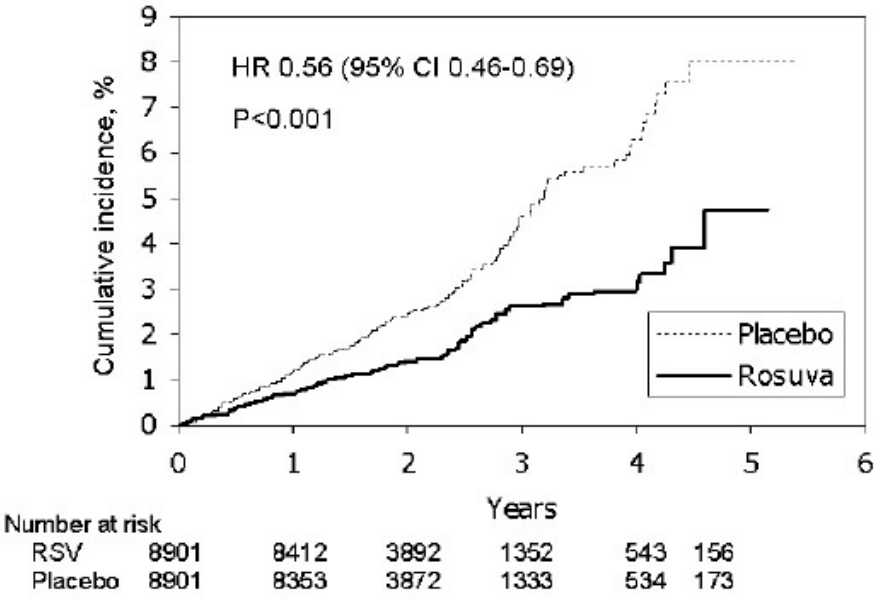
In the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study, the effect of CRESTOR on the occurrence of major cardiovascular (CV) disease events was assessed in 17,802 men (≥50 years) and women (≥60

years) who had no clinically evident cardiovascular disease, LDL-C levels <130 mg/dL and hsCRP 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%). Patients had a median baseline LDL-C of 108 mg/dL and hsCRP of 4.3 mg/L. Patients were randomly assigned to placebo (n=8901) or CRESTOR 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 CRESTOR-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.

CRESTOR 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 1). 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 1. Time to First Occurrence of Major Cardiovascular Events in JUPITER

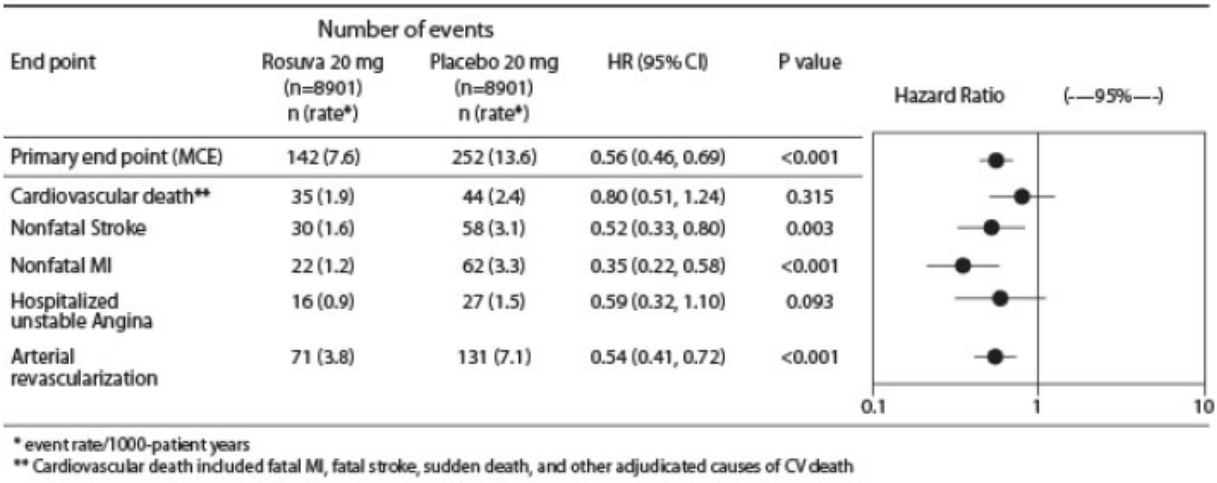


The individual components of the primary end point are presented in Figure 3. CRESTOR significantly reduced the risk of nonfatal myocardial infarction, nonfatal stroke, and arterial revascularization procedures. There were no significant treatment differences between the CRESTOR and placebo groups for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

CRESTOR 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 CRESTOR-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 CRESTOR-treated subjects).

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

Figure 2. Major CV Events by Treatment Group in JUPITER



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

Primary Hyperlipidemia in Adults

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

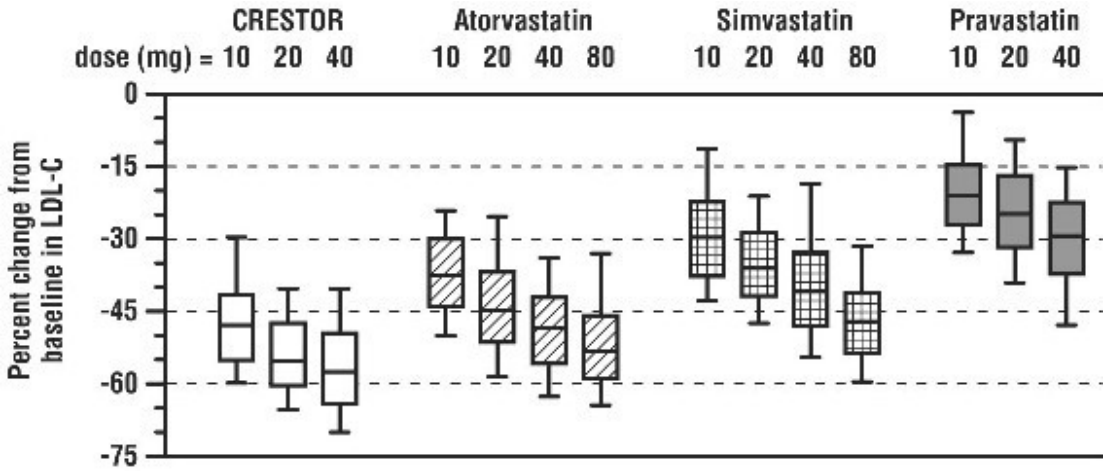
In a multicenter, double-blind, placebo-controlled study in patients with hyperlipidemia, CRESTOR given as a single daily dose (5 to 40 mg) for 6 weeks significantly reduced Total-C, LDL-C, non-HDL-C, and ApoB, across the dose range (Table 10).

Table 10: Lipid-modifying Effect of CRESTOR in Adult 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

CRESTOR was compared with the statins (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 3 and Table 11).

Figure 3. Percent LDL-C Change by Dose of CRESTOR, Atorvastatin, Simvastatin, and Pravastatin at Week 6 in Adult 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 11: Percent Change in LDL-C by Dose of CRESTOR, Atorvastatin, Simvastatin, and Pravastatin From Baseline to Week 6 (LS Mean[1]) in Adult Patients with Hyperlipidemia or Mixed Dyslipidemia (Sample Sizes Ranging from 156–167 Patients Per Group)

	Treatment Daily Dose			
Treatment	**10 mg**	**20 mg**	**40 mg**	**80 mg**
CRESTOR	-46[2]	-52[3]	-55[4]	---
Atorvastatin	-37	-43	-48	-51
Simvastatin	-28	-35	-39	-46
Pravastatin	-20	-24	-30	---

[1] Corresponding standard errors are approximately 1.00.
[2] CRESTOR 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. ($p<0.002$)
[3] CRESTOR 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. ($p<0.002$)
[4] CRESTOR 40 mg reduced LDL-C significantly more than atorvastatin 40 mg; pravastatin 40 mg; simvastatin 40 mg, and 80 mg. ($p<0.002$)

Slowing of the Progression of Atherosclerosis

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

Pregnancy

Advise pregnant patients and patients who can become pregnant of the potential risk to a fetus. Advise patients to inform their healthcare provider of a known or suspected pregnancy to discuss if CRESTOR should be discontinued *[see Use in Specific Populations (8.1)]*.

Lactation

Advise patients that breastfeeding during treatment with CRESTOR is not recommended *[see Use in Specific Populations (8.2)]*.

Concomitant Use of Antacids

When taking CRESTOR with an aluminum and magnesium hydroxide combination antacid, the antacid should be taken at least 2 hours after CRESTOR administration *[see Drug Interactions (7.2)]*.

Missed Doses

If a dose is missed, advise patients not take an extra dose. Just resume the usual schedule *[see General Dosage and Administration Information (2.1)]*.

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PATIENT INFORMATION
CRESTOR® (Kres-tor)
rosuvastatin
Tablets

Read this Patient Information carefully before you start taking CRESTOR and each time you get a refill. If you have any questions about CRESTOR, ask your doctor. Only your doctor can determine if CRESTOR is right for you.

What is CRESTOR?

CRESTOR is a prescription medicine that contains a cholesterol-lowering medicine called rosuvastatin.

- CRESTOR is used to:
  - reduce the risk of stroke, heart attack, and the need for procedures to improve blood flow to the heart called arterial revascularization in adults who do not have known heart disease but do have certain additional risk factors.
- CRESTOR is used along with diet to:
  - lower the level of low-density lipoprotein (LDL) cholesterol or "bad" cholesterol in adults with primary hyperlipidemia.
  - slow the buildup of fatty deposits (plaque) in the walls of blood vessels.
  - treat adults and children 8 years of age and older with high blood cholesterol due to heterozygous familial hypercholesterolemia (an inherited condition that causes high levels of LDL).
  - along with other cholesterol lowering treatments or alone if such treatments are unavailable in adults and children 7 years of age and older with homozygous familial hypercholesterolemia (an inherited condition that causes high levels of LDL).
  - treat adults with a type of high cholesterol called primary dysbetalipoproteinemia (type III hyperlipoproteinemia).
  - lower the level of fat in your blood (triglycerides) in adults with hypertriglyceridemia.

The safety and effectiveness of CRESTOR has not been established in children younger than 8 years of age with heterozygous familial hypercholesterolemia or children younger than 7 years of age with homozygous familial hypercholesterolemia or in children with other types of hyperlipidemias (other than HeFH or HoFH).

Who should not take CRESTOR?

Do not take CRESTOR if you:

- have liver problems.
- are allergic to rosuvastatin or any of the ingredients in CRESTOR. See the end of this leaflet for a complete list of ingredients in CRESTOR. Symptoms of allergic reactions include rash, itching, hives, and swelling.

What should I tell my doctor before and while taking CRESTOR?

Tell your doctor if you:

- have unexplained muscle aches or weakness.
- have or have had kidney problems.
- have or have had liver problems.
- drink more than 2 glasses of alcohol daily.
- have thyroid problems.
- are 65 years of age or older.
- are of Asian descent.
- are pregnant or think you may be pregnant, or are planning to become pregnant. If you become pregnant while taking CRESTOR, call your healthcare provider right away to discuss your CRESTOR treatment.

- are breastfeeding. CRESTOR can pass into your breast milk. Breastfeeding is not recommended while taking CRESTOR.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Taking CRESTOR with certain other medicines may affect each other causing side effects. CRESTOR may affect the way other medicines work, and other medicines may affect how CRESTOR works.

Especially tell your doctor if you take:

- cyclosporine (a medicine for your immune system)
- gemfibrozil (a fibric acid medicine for lowering cholesterol)
- fostamatinib (a medicine used to treat low platelet counts)
- febuxostat (a medicine used to treat and prevent high blood levels of uric acid)
- teriflunomide (a medicine used to treat relapsing remitting multiple sclerosis)
- capmatinib (a medicine for the treatment of non-small cell lung cancer)
- tafamidis (used to treat cardiomyopathy [enlarged and thickened heart muscle])
- darolutamide (a medicine for the treatment of prostate cancer)
- regorafenib (a medicine used to treat cancer of the colon and rectum)
- enasidenib (a medicine used to treat acute myeloid leukemia)
- anti-viral medicines including certain HIV or hepatitis C virus drugs such as:
    - lopinavir, ritonavir, fosamprenavir, tipranavir, atazanavir, simeprevir
    - combination of
        - sofosbuvir/velpatasvir/voxilaprevir
        - dasabuvir/ombitasvir/paritaprevir/ritonavir
        - elbasvir/grazoprevir
        - sofosbuvir/velpatasvir
        - glecaprevir/pibrentasvir **and**
    - all other combinations with ledipasvir including ledipasvir/sofosbuvir
- certain anti-fungal medicines (such as itraconazole, ketoconazole and fluconazole)
- coumarin anticoagulants (medicines that prevent blood clots, such as warfarin)
- niacin or nicotinic acid
- fibric acid derivatives (such as fenofibrate)
- colchicine (a medicine used to treat gout)

Ask your doctor or pharmacist for a list of these medicines if you are not sure. Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get new medicine.

How should I take CRESTOR?

- Take CRESTOR exactly as your doctor tells you to take it.
- Take CRESTOR, by mouth, 1 time each day. Swallow the tablet whole.
- CRESTOR can be taken at any time of day, with or without food.
- **Do not** change your dose or stop CRESTOR without talking to your doctor, even if you are feeling well.
- Your doctor may do blood tests to check your cholesterol levels before and during your treatment with CRESTOR. Your doctor may change your dose of CRESTOR if needed.
- Your doctor 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 your next dose at your normal scheduled time. **Do not take** an extra dose of CRESTOR**.**
- If you take too much CRESTOR or overdose, call your doctor or go to the nearest hospital emergency room right away.

What are the possible side effects of CRESTOR?

CRESTOR may cause serious side effects, including:

- **Muscle pain, tenderness and weakness (myopathy).** Muscle problems, including muscle breakdown, can be serious in some people and rarely cause kidney damage that can lead to death. Tell your doctor right away if:
  - you have unexplained muscle pain, tenderness, or weakness, especially if you have a fever or feel more tired than usual, while you take CRESTOR.
  - you have muscle problems that do not go away even after your doctor has told you to stop taking CRESTOR. Your doctor may do further tests to diagnose the cause of your muscle problems.

Your chances of getting muscle problems are higher if you:

- are taking certain other medicines while you take CRESTOR
- are 65 years of age or older
- have thyroid problems (hypothyroidism) that are not controlled
- have kidney problems
- are taking higher doses of CRESTOR

- **Liver problems.** Your doctor may 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
- **Protein and blood in the urine.** CRESTOR may cause you to have protein and blood in your urine. If you develop protein or blood in your urine, your doctor may decrease your dose of CRESTOR.
- **Increase in blood sugar (glucose) levels**. CRESTOR may cause an increase in your blood sugar levels.

The most common side effects may include headache, muscle aches and pains, abdominal pain, weakness, and nausea.

Tell your doctor if you have any side effect that bothers you or that does not go away.

For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store CRESTOR?

- Store CRESTOR at room temperature, between 68°F to 77°F (20°C to 25°C) and in a dry place.
- Safely throw away medicine that is out of date or no longer needed.

Keep CRESTOR and all medicines out of the reach of children.

General Information about the safe and effective use of CRESTOR

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. 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.

You can ask your pharmacist or doctor for information about CRESTOR that is written for health professionals.

What are the Ingredients in CRESTOR?

Active Ingredient: rosuvastatin as rosuvastatin calcium

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

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For more information, go to the CRESTOR website at www.crestor.com or call 1-800-CRESTOR

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