HIGHLIGHTS OF PRESCRIBING INFORMATION
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

----------RECENT MAJOR CHANGES ----------

Indications and Usage, Slowing of the Progression of Atherosclerosis (1.4)	11/2007
Dosage and Administration,	
Slowing of the Progression of Atherosclerosis (2.2)	11/2007
Use with Cyclosporine or Lopinavir/Ritonavir (2.5)	07/2007
Warnings and Precautions, Skeletal Muscle Effects (5.1)	07/2007

----------INDICATIONS AND USAGE----------
CRESTOR is an HMG Co-A reductase inhibitor indicated for:
- patients with primary hyperlipidemia and mixed dyslipidemia as an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and TG levels and to increase HDL-C (1.1)
- patients with hypertriglyceridemia as an adjunct to diet (1.2)
- patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C, total-C, and ApoB (1.3)
- slowing the progression of atherosclerosis as part of a treatment strategy to lower total-C and LDL-C as an adjunct to diet (1.4)

Limitations of use (1.5):
- Effect of CRESTOR on cardiovascular morbidity and mortality has not been determined.
- CRESTOR has not been studied in Fredrickson Type I, III, and V dyslipidemias.

----------DOSAGE AND ADMINISTRATION----------
- CRESTOR can be taken with or without food, at any time of day. (2.1)
- Dose range: 5-40 mg once daily. Use 40 mg dose only for patients not reaching LDL-C goal with 20 mg. (2.1)
- **Hyperlipidemia, mixed dyslipidemia, hypertriglyceridemia, and atherosclerosis**: Starting dose 10 mg. Consider 20 mg starting dose for patients with LDL-C>190 mg/dL and aggressive lipid targets. (2.2)
- **HoFH**: Starting dose 20 mg. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 5 mg, 10 mg, 20 mg, and 40 mg (3)

----------CONTRAINDICATIONS----------
- Known hypersensitivity to product components (4)
- Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels (4)
- Women who are pregnant or may become pregnant (4, 8.1)
- Nursing mothers (4, 8.3)

----------WARNINGS AND PRECAUTIONS----------
- **Skeletal muscle effects (e.g., myopathy and rhabdomyolysis)**: Risks increase with use of 40 mg dose, advanced age (≥65), hypothyroidism, renal impairment, and combination use with cyclosporine, lopinavir/ritonavir, or certain other lipid-lowering drugs. Advise patients to promptly report unexplained muscle pain, tenderness, or weakness and discontinue CRESTOR if signs or symptoms appear (5.1)
- **Liver enzyme abnormalities and monitoring:** Persistent elevations in hepatic transaminases can occur. Monitor liver enzymes before and during treatment. (5.2)

----------ADVERSE REACTIONS----------
Most frequent adverse reactions (rate ≥ 2%) are headache, myalgia, abdominal pain, asthenia, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------
- **Cyclosporine**: Combination increases rosuvastatin exposure. Limit CRESTOR to 5 mg once daily. (2.5, 7.1)
- **Gemfibrozil**: Combination should be avoided. If used together, limit CRESTOR dose to 10 mg once daily. (2.6, 5.1, 7.2)
- **Lopinavir/Ritonavir**: Combination increases rosuvastatin exposure. Limit CRESTOR dose to 10 mg once daily. (2.5, 5.1, 7.3)
- **Coumarin anti-coagulants:** Combination prolongs INR. Achieve stable INR prior to starting CRESTOR. Monitor INR frequently until stable upon initiation or alteration of CRESTOR therapy. (5.3, 7.4)
- **Concomitant lipid-lowering therapies:** Use with fibrates and niacin products may increase the risk of skeletal muscle effects. (2.6, 5.1, 7.5, 7.6)

----------USE IN SPECIFIC POPULATIONS----------
- **Pediatric use**: Safety and effectiveness not established. (8.4)
- **Severe renal impairment (not on hemodialysis)**: Starting dose is 5 mg, not to exceed 10 mg. (2.7, 5.1, 8.6)
- **Asian population**: Consider 5 mg starting dose. (2.4, 8.8)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 11/2007

***FULL PRESCRIBING INFORMATION: CONTENTS**

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Hyperlipidemia and Mixed Dyslipidemia

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 non-pharmacological interventions alone has been inadequate.

1.2 Hypertriglyceridemia

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

1.3 Homozygous Familial Hypercholesterolemia

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.

1.4 Slowing of the Progression of Atherosclerosis

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.

1.5 Limitations of Use

The effect of CRESTOR on cardiovascular morbidity and mortality has not been determined.

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

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

The dose range for CRESTOR is 5 to 40 mg orally once daily.

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.

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)].

2.2 Hyperlipidemia, Mixed Dyslipidemia, Hypertriglyceridemia and Slowing of the Progression of Atherosclerosis

The recommended starting dose of CRESTOR is 10 mg once daily. For patients with marked hyperlipidemia (LDL-C > 190 mg/dL) and aggressive lipid targets, a 20 mg starting dose may be considered.

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

2.3 Homozygous Familial Hypercholesterolemia

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

2.4 Dosage in Asian Patients

Initiation of CRESTOR therapy with 5 mg once daily should be considered for Asian patients. [*see Use in Specific Populations* (8.8) *and Clinical Pharmacology* (12.3)].

2.5 Use with Cyclosporine or Lopinavir/Ritonavir

In patients taking cyclosporine, the dose of CRESTOR should be limited to 5 mg once daily [see *Warnings and Precautions* (5.1) *and Drug Interactions* (7.1)]. In patients taking a combination of lopinavir and ritonavir, the dose of CRESTOR should be limited to 10 mg once daily [*see Warnings and Precautions* (5.1) *and Drug Interactions* (7.3)].

2.6 Concomitant Lipid-Lowering Therapy

The risk of skeletal muscle effects may be enhanced when CRESTOR is used in combination with niacin or fenofibrate; a reduction in CRESTOR dosage should be considered in this setting. [*see Warnings and Precautions* (5.1) *and Drug Interactions* (7.5, 7.6)]

Combination therapy with gemfibrozil should be avoided because of an increase in CRESTOR exposure with concomitant use; if CRESTOR is used in combination with gemfibrozil, the dose of CRESTOR should be limited to 10 mg once daily [*see Warnings and Precautions* (5.1) *and Drug Interactions* (7.2)].

2.7 Dosage in Patients With Severe Renal Impairment

For patients with severe renal impairment (CL_{cr} <30 mL/min/1.73 m^2) 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)].

3 DOSAGE FORMS AND 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.

4 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)].

5 WARNINGS AND PRECAUTIONS

5.1 Skeletal Muscle Effects

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 ≥ 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, or lopinavir/ritonavir. [*see Dosage and Administration* (2) *and Drug Interactions* (7)].

CRESTOR therapy should be discontinued if markedly elevated creatinine 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). All patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

5.2 Liver Enzyme Abnormalities and Monitoring

It is recommended that liver enzyme tests be performed before and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter.

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.

Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of CRESTOR is recommended.

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)]

5.3 Concomitant Coumarin Anticoagulants

Caution should be exercised when anticoagulants are given in conjunction with CRESTOR because of the potentiation of coumarin-type anti-coagulants 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)]

5.4 Proteinuria and Hematuria

In the CRESTOR clinical trial program, dipstick-positive proteinuria and microscopic hematuria were observed among CRESTOR treated patients. This finding was 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.

5.5 Endocrine Effects

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