**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,~~
~~Pediatric Patients 10 to 17 years of age with Heterozygous Familial Hypercholesterolemia (HeFH) (1.1) 10/200~~
~~Dosage and Administration,~~
~~HeFH in Pediatric Patients (10 to 17 years of age) (2.2) 10/2009~~
~~Dosage and Administration, Use with Cyclosporine, Lopinavir/Ritonavir or Atazanavir/Ritonavir (2.5) 01/2010~~
~~Warnings and Precautions, Skeletal muscle effects (e.g., myopathy and rhabdomyolysis) (5.1) 01/2010~~
~~Indications and Usage,~~
~~Primary Prevention of Cardiovascular Disease (1.6) 02/2010~~

**----------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 primary dysbetalipoproteinemia (Type III hyperlipoproteinemia) as an adjunct to diet (1.3)
- patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C, total-C, and ApoB (1.4)
- slowing the progression of atherosclerosis as part of a treatment strategy to lower total-C and LDL-C as an adjunct to diet (1.5)
- pediatric patients 10 to 17 years of age with heterozygous familial hypercholesterolemia (HeFH) to reduce elevated total-C, LDL-C and ApoB after failing an adequate trial of diet therapy (1.1)
- risk reduction of MI, stroke, and arterial revascularization procedures in patients without clinically evident CHD, but with multiple risk factors (1.6)

Limitations of use (1.7):
- CRESTOR has not been studied in Fredrickson Type I 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)
- **HoFH**: Starting dose 20 mg. (2.3)
- In pediatric patients 10 to 17 years of age with HeFH, the usual dose range is 5-20 mg/day; doses greater than 20 mg have not been studied in this patient population. (2.2)

**----------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 atazanavir/ritonavir~~, or certain other lipid-lowering drugs~~. Advise patients to promptly report to their physician unexplained muscle pain, tenderness, or weakness and discontinue CRESTOR if signs or symptoms appear. (5.1, 7.5, 7.6)
- **Liver enzyme abnormalities~~ and monitoring~~:** Persistent elevations in hepatic transaminases can occur. ~~Monitor~~Perform liver enzyme~~s~~ tests before initiating therapy and ~~during treatment~~as clinically indicated thereafter.(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 dose 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 or atazanavir/ritonavir**: Combination increases rosuvastatin exposure. Limit CRESTOR dose to 10 mg once daily. (2.5, 5.1, 7.3)
- **Coumarin anticoagulants:** 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~~ or lipid-modifying doses (≥1 g/day) of niacin ~~products may~~ increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with CRESTOR. (~~2.6,~~ 5.1, 7.5, 7.6)

**----------USE IN SPECIFIC POPULAIONS----------**
- **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: ~~June 2010~~Month, 2012**

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# 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 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.

### 1.2 Hypertriglyceridemia

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

### 1.3 Primary Dysbetalipoproteinemia (Type III Hyperlipoproteinemia)

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



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### 1.4 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.

### 1.5 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.

### 1.6 Primary Prevention of Cardiovascular Disease

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

### 1.7 Limitations of Use

CRESTOR has not been studied in Fredrickson Type I 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. 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.



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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)].

**2.2 Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10 to 17 years of age)**

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.

**2.3 Homozygous Familial Hypercholesterolemia**

The recommended starting dose of CRESTOR is 20 mg once daily. Response to therapy should be estimated from preapheresis 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, Lopinavir/Ritonavir or Atazanavir/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 or atazanavir and ritonavir, the dose of CRESTOR should be limited to



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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[10]; 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)].~~

**2.6~~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



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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).



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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 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 to their physician 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~~CRESTOR ~~and any elevation of dose~~, and if signs or symptoms of liver injury occur ~~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.

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



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and/or hyperbilirubinemia or jaundice occurs during treatment with CRESTOR, promptly interrupt therapy. If an alternate etiology is not found, do not restart CRESTOR.~~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 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)].

**5.4 Proteinuria and Hematuria**

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.

**5.5 Endocrine Effects**



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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.

## 6 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 ≥ 2%) in the CRESTOR controlled clinical trial database of 5394 patients were:

- headache
- myalgia
- abdominal pain



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- asthenia
- nausea

### 6.1 Clinical Studies Experience

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 ≥ 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 ≥ 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 |

* Adverse reactions by COSTART preferred term.

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.



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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 ≥ 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<br><br>N=700 | Placebo<br><br>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 |

* Adverse reactions by MedDRA preferred term.

† Frequency recorded as abnormal laboratory value.

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



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(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<br><br>N=8901 | Placebo<br><br>N=8901 |
|---|---|---|
| Myalgia | 7.6 | 6.6 |
| Arthralgia | 3.8 | 3.2 |
| Constipation | 3.3 | 3.0 |
| Nausea | 2.4 | 2.3 |

* Treatment-emergent adverse reactions by MedDRA preferred term.

**6.2 Pediatric patients 10 to 17 years of age**

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 ~~Special~~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.



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### 6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of CRESTOR: arthralgia, fatal and non-fatal hepatic failure, hepatitis, jaundice, ~~memory loss,~~ depression, and sleep disorders (including insomnia and nightmares). 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 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).

## 7 DRUG INTERACTIONS

### 7.1 Cyclosporine

Cyclosporine significantly increased rosuvastatin exposure. Therefore, in patients taking cyclosporine, therapy should be limited to CRESTOR 5 mg once daily [*see Dosage and Administration* (2.5), *Warnings and Precautions* (5.1), and *Clinical Pharmacology* (12.3)].

### 7.2 Gemfibrozil

Gemfibrozil significantly increased rosuvastatin exposure. Therefore, combination therapy with CRESTOR and gemfibrozil should be avoided. –If used, do not exceed CRESTOR 10 mg once daily —[*see* ~~*Dosage and Administration* (2.6) and~~ *Clinical Pharmacology* (12.3)].



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### 7.3 Protease Inhibitors

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 3 – Clinical Pharmacology (12.3)*]. For these combinations the dose of CRESTOR should be limited to 10 mg. 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)].

### 7.4 Coumarin Anticoagulants

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)].

### 7.5 Niacin

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~~a reduction in CRESTOR dosage should be considered in this setting~~ [*see Warnings and Precautions* (5.1)].



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### 7.6 Fenofibrate

When CRESTOR was coadministered with fenofibrate, no clinically significant increase in the AUC of rosuvastatin or fenofibrate was observed. ~~The benefit of further alterations in lipid levels by the combined use of CRESTOR with fibrates should be carefully weighed against the potential risks of this combination~~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)].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

**Teratogenic effects: Pregnancy Category X.**

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



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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.

**8.3 Nursing Mothers**

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)].

**8.4 Pediatric Use**

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



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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.

### 8.5 Geriatric Use

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)].

### 8.6 Renal Impairment

Rosuvastatin exposure is not influenced by mild to moderate renal impairment ($CL_{cr} \geq 30$ mL/min/1.73 $m^2$); 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 $m^2$) not requiring hemodialysis [*see Dosage and Administration* (2.7), *Warnings and Precautions* (5.1) and *Clinical Pharmacology* (12.3)].



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### 8.7 Hepatic Impairment

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)].

### 8.8 Asian Patients

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)].

## 10 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.

## 11 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:



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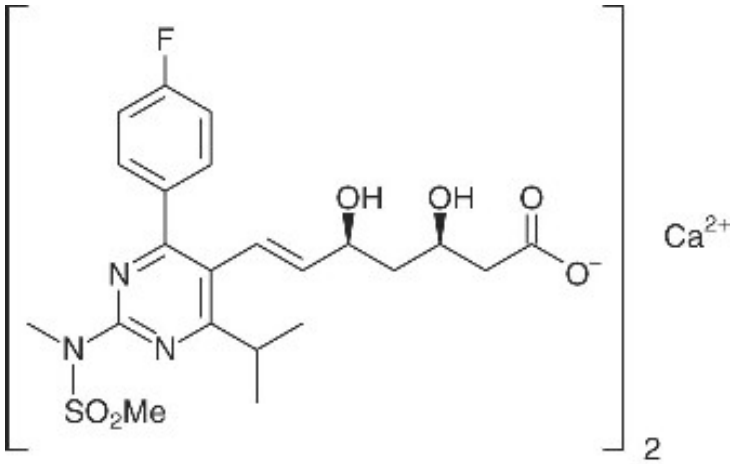


The empirical formula for rosuvastatin calcium is $(C_{22}H_{27}FN_3O_6S)_2Ca$ and the molecular weight is 1001.14. Rosuvastatin calcium is a white amorphous powder that is sparingly soluble in water and methanol, and slightly soluble in ethanol. Rosuvastatin calcium is a hydrophilic compound with a 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 ~~I~~inactive ~~I~~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.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

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



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synthesis of VLDL, which reduces the total number of VLDL and LDL particles.

### 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 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.



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- ***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 $m^2$) 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 $m^2$) not receiving hemodialysis compared with healthy subjects ($CL_{cr} > 80$ mL/min/1.73 $m^2$).

- ***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.



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***Drug-Drug Interactions:***

**Cytochrome P450 3A4**

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

**Table 4. Effect of Coadministered Drugs on Rosuvastatin Systemic Exposure**

| **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-fold† | ↑11-fold† |
| Gemfibrozil 600 mg BID for 7 days | 80 mg | ↑ 1.9-fold† | ↑ 2.2-fold† |
| Lopinavir/ritonavir combination 400 mg/100 mg BID for 10 days | 20 mg QD for 7 days | ↑ 2-fold† | ↑ 5-fold† |
| Atazanavir/ritonavir combination 300 mg/100 mg QD for 7 days | 10 mg | ↑ 3-fold† | ↑ 7-fold† |
| Tipranavir/ritonavir combination 500 mg/200mg BID for 11 days | 10 mg | ↑ 26% | ↑ 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 | ↑ 7% | ↑21% |
| Aluminum & magnesium hydroxide combination antacid<br>Administered simultaneously<br>Administered 2 hours apart | <br><br>40 mg<br>40 mg | <br><br>↓ 54%†<br>↓ 22% | <br><br>↓ 50%†<br>↓ 16% |
| Erythromycin 500 mg QID for 7 days | 80 mg | ↓ 20% | ↓ 31% |
| Ketoconazole 200 mg BID for 7 days | 80 mg | ↑ 2% | ↓ 5% |
| Itraconazole 200 mg QD for 5 days | 10 mg<br>80 mg | ↑ 39%<br>↑ 28% | ↑ 36%<br>↑ 15% |
| Fluconazole 200 mg QD for 11 days | 80 mg | ↑ 14% | ↑ 9% |

*Single dose unless otherwise noted

**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.

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



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**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%<br>S-Warfarin ↑6% | R-Warfarin ↓ 1%<br>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%<br>NG ↑ 34% | EE ↑ 25%<br>NG ↑ 23% |

EE = ethinyl estradiol, NG = norgestrel
*Clinically significant pharmacodynamic effects [*see Warnings and Precautions* (5.4)]

## 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, 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.



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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.

### 13.2 Animal Toxicology and/or Pharmacology

**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 ≥ 12 times the human exposure at 40 mg/day based on body surface area.



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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 ≤ 25 mg/kg/day or in rabbits ≤ 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.



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## 14 CLINICAL STUDIES

### 14.1 Hyperlipidemia and Mixed Dyslipidemia

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).



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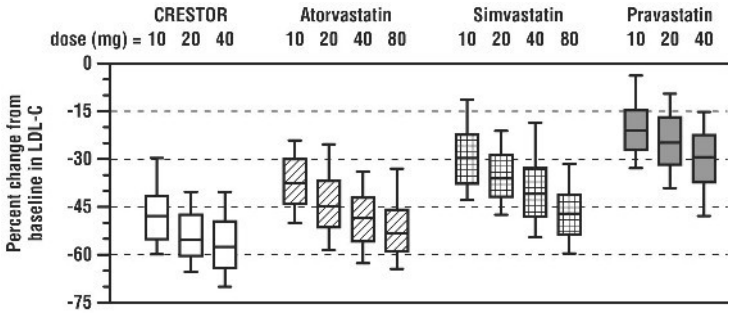
**Figure 1. Percent LDL-C Change by Dose of CRESTOR, Atorvastatin, Simvastatin, and Pravastatin at Week 6 in Patients with Hyperlipidemia or Mixed Dyslipidemia**




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 Daily Dose** | | | |
|---|---|---|---|---|
| **Treatment** | **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 | --- |

[*] Corresponding standard errors are approximately 1.00

[†] 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. ($p<0.002$)

[‡] 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. ($p<0.002$)

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

## 14.2 Heterozygous Familial Hypercholesterolemia

*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.



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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* (95% CI) |
|---|---|---|---|
| Week 6 | 20 mg | -47% (-49%, -46%) | -38% (-40%, -36%) |
| Week 12 | 40 mg | -55% (-57%, -54%) | -47% (-49%, -45%) |
| Week 18 | 80 mg | NA | -52% (-54%, -50%) |

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

### 14.3 Hypertriglyceridemia

*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, | 3 (-38, 33) | 8 (-8, 24) | 22 (-5, 50) | 17 (-14, 63) |



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| Dose | Placebo (n=26) | CRESTOR 5 mg (n=25) | CRESTOR 10 mg (n=23) | CRESTOR 20 mg (n=27) | CRESTOR 40 mg (n=25) |
|---|---|---|---|---|---|
| | 18) | | | | |

**14.4 Primary Dysbetalipoproteinemia (Type III Hyperlipoproteinemia)**

In a randomized, multicenter, double-blind crossover study, 32 patients (27 with ε2/ε2 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 | 11.2 |



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| | | | |
|---|---|---|---|
| | | (1.9, 12.3) | (8.3, 20.5) |
| RLP-C | 82.0 | -56.4<br>(-67.1, -49.0) | -64.9<br>(-74.0, -56.6) |
| Apo-E | 16.0 | -42.9<br>(-46.3, -33.3) | -42.5<br>(-47.1, -35.6) |

### 14.5 Homozygous Familial Hypercholesterolemia

*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.

### 14.6 Pediatric Patients with Heterozygous Familial Hypercholesterolemia

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.



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**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[a] | ApoB |
|---|---|---|---|---|---|---|
| **Placebo** | 46 | -1% | +7% | 0% | -7% | -2% |
| **5** | 42 | -38% | +4%[b] | -30% | -13%[b] | -32% |
| **10** | 44 | -45% | +11%[b] | -34% | -15%[b] | -38% |
| **20** | 44 | -50% | +9%[b] | -39% | -16%[b] | -41% |

[a] Median percent change
[b] Difference from placebo not statistically significant

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.

### 14.7 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 <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



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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.

**14.8 Primary Prevention of Cardiovascular Disease**

In the **J**ustification for the **U**se of Statins in **P**rimary Prevention: An **I**ntervention **T**rial **E**valuating **R**osuvastatin (JUPITER) study, 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,



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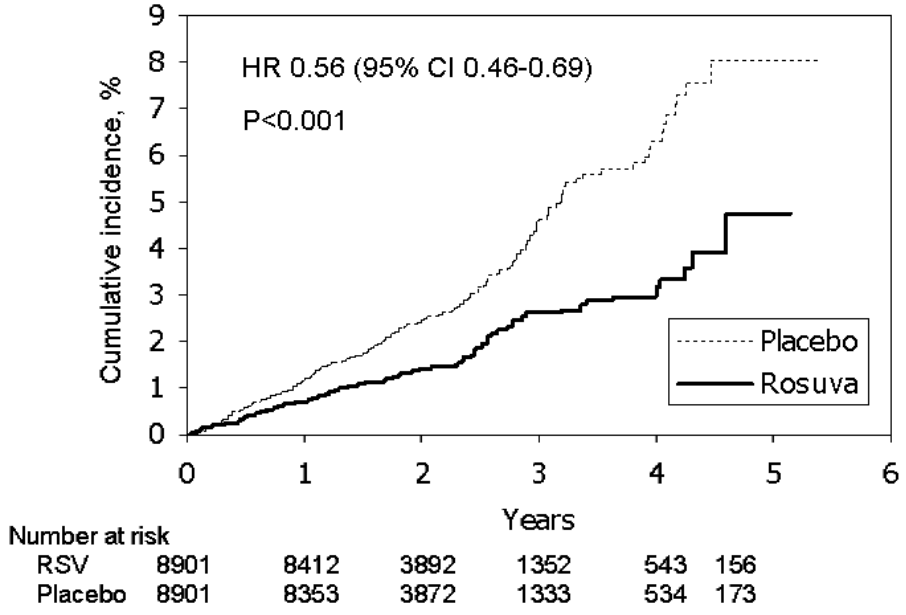
nonfatal stroke, hospitalization for unstable angina or an arterial revascularization procedure.

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**



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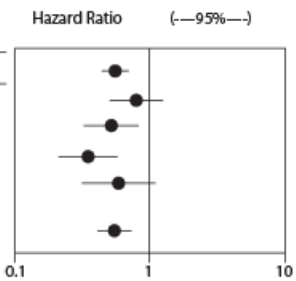
The individual components of the primary end point are presented in Figure 3. Rosuvastatin significantly reduced the risk of nonfatal myocardial infarction, nonfatal stroke, and arterial revascularization procedures. There were no significant treatment differences between the rosuvastatin and placebo 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 ≥ 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**

| End point | Number of events: Rosuva 20 mg (n=8901) n (rate*) | Number of events: Placebo 20 mg (n=8901) n (rate*) | HR (95% CI) | P value |
|---|---|---|---|---|
| Primary end point (MCE) | 142 (7.6) | 252 (13.6) | 0.56 (0.46, 0.69) | <0.001 |
| Cardiovascular death** | 35 (1.9) | 44 (2.4) | 0.80 (0.51, 1.24) | 0.315 |
| Nonfatal Stroke | 30 (1.6) | 58 (3.1) | 0.52 (0.33, 0.80) | 0.003 |
| Nonfatal MI | 22 (1.2) | 62 (3.3) | 0.35 (0.22, 0.58) | <0.001 |
| Hospitalized unstable Angina | 16 (0.9) | 27 (1.5) | 0.59 (0.32, 1.10) | 0.093 |
| Arterial revascularization | 71 (3.8) | 131 (7.1) | 0.54 (0.41, 0.72) | <0.001 |




* event rate/1000-patient years
** Cardiovascular death included fatal MI, fatal stroke, sudden death, and other adjudicated causes of CV death

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).



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## 16 HOW SUPPLIED/STORAGE AND HANDLING

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, 20-25ºC (68-77ºF) [see USP Controlled Room Temperature]. Protect from moisture.

## 17 PATIENT COUNSELING INFORMATION

### 17.1 Skeletal Muscle Effects

Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

### 17.2 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.



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### 17.3 Pregnancy

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.

### 17.4 Liver Enzymes

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