

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021366Orig1s024

Trade Name: CRESTOR

Generic Name: Rosuvastatin Calcium

Sponsor: AstraZeneca Pharmaceuticals LP

Approval Date: 02/28/2012

Indications:

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; patients with hypertriglyceridemia as an adjunct to diet; patients with primary dysbetalipoproteinemia (Type III hyperlipoproteinemia) as an adjunct to diet; patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C, total-C, and ApoB; slowing the progression of atherosclerosis as part of a treatment strategy to lower total-C and LDL-C as an adjunct to diet; 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; risk reduction of MI, stroke, and arterial revascularization procedures in patients without clinically evident CHD, but with multiple risk factors.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
021192Orig1s019

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
021366Orig1s024

APPROVAL LETTER



NDA 21366/S-024

SUPPLEMENT APPROVAL

AstraZeneca Pharmaceuticals LP
US Agent for IPR Pharmaceuticals, Inc.
Attention: Pat DeFeo, MS
1800 Concord Pike, P. O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. DeFeo:

Please refer to your Supplemental New Drug Application (sNDA) dated September 28, 2011, received September 28, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for CRESTOR (rosuvastatin calcium) Tablets 5 mg, 10 mg, 20 mg, and 40 mg.

We acknowledge receipt of your amendments dated December 20, 2011, and February 7, 2012.

We also refer to our letter dated August 11, 2011, requesting that sponsors of HMG-CoA reductase inhibitor (statin) drugs, modify their labeling based on our comprehensive review of clinical trial data, Adverse Event Reporting System (AERS) reports, the published literature, and the labels of other approved drugs containing information on statin coadministration.

This "Prior Approval" supplemental new drug application provides for revisions to the **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS** sections of the Highlights of Prescribing Information section and changes to the **DOSAGE AND ADMINISTRATION**, **WARNINGS AND PRECAUTIONS**, **ADVERSE REACTIONS**, and **PATIENT COUNSELING INFORMATION** sections of the Full Prescribing Information sections of the CRESTOR (rosuvastatin) package insert, and corresponding revisions to the CRESTOR (rosuvastatin) patient package insert.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content

of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Margaret Simoneau, M.S., R.Ph., Regulatory Project Manager, at (301) 796-1295.

Sincerely,

{See appended electronic signature page}

Amy G. Egan, M.D., M.P.H.
Deputy Director for Safety
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY G EGAN
02/28/2012

**CENTER FOR DRUG EVALUATION AND
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APPLICATION NUMBER:
021366Orig1s024

LABELING

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

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. 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:** Persistent elevations in hepatic transaminases can occur. Perform liver enzyme tests before initiating therapy and as clinically indicated thereafter. (5.2)

ADVERSE REACTIONS

Most frequent adverse reactions (rate $\geq 2\%$) 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. (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 or lipid-modifying doses (≥ 1 g/day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with CRESTOR. (5.1, 7.5, 7.6)

USE IN SPECIFIC POPULATIONS

- 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)

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Revised: 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).

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.

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

10 mg once daily [*see Warnings and Precautions (5.1) and Drug Interactions (7.3)*].

2.6 Dosage in Patients With Severe Renal Impairment

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

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 \geq 65 years, inadequately treated hypothyroidism, renal impairment).

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

CRESTOR therapy should be discontinued if markedly elevated 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

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

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

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

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

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

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

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 $\geq 2\%$) in the CRESTOR controlled clinical trial database of 5394 patients were:

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

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

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

* 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.

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

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

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

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

* 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 (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 $\geq 2\%$ of patients and at a rate greater than placebo are shown in Table 3.

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

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

* 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 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.

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, 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 Clinical Pharmacology (12.3)*].

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 [*see Warnings and Precautions* (5.1)].

7.6 Fenofibrate

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

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 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 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 m²); however, exposure to rosuvastatin is increased to a clinically significant extent in patients with severe renal impairment who are not receiving hemodialysis. CRESTOR dosing should be adjusted in patients with severe renal impairment ($CL_{cr} < 30$ mL/min/1.73 m²) not requiring hemodialysis [see *Dosage and Administration* (2.7), *Warnings and Precautions* (5.1) and *Clinical Pharmacology* (12.3)].

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

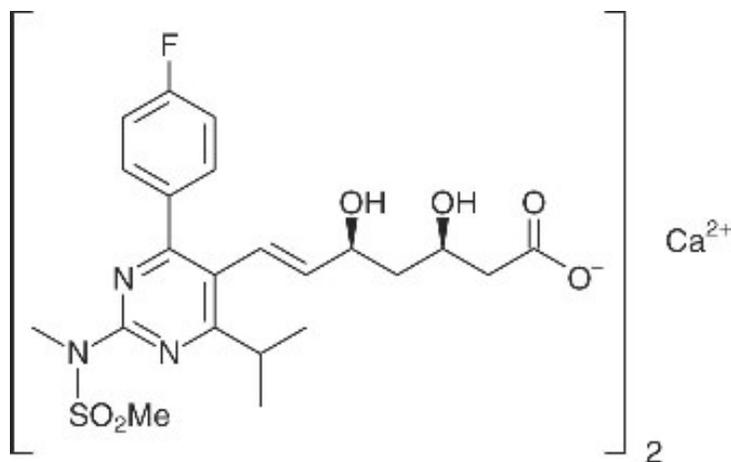
There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Hemodialysis does not significantly enhance clearance of rosuvastatin.

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:



The empirical formula for rosuvastatin calcium is (C₂₂H₂₇FN₃O₆S)₂Ca and the molecular weight is 1001.14. Rosuvastatin calcium is a white amorphous powder that is sparingly soluble in water and methanol, and slightly soluble in ethanol. Rosuvastatin calcium is a hydrophilic compound with a partition coefficient (octanol/water) of 0.13 at pH of 7.0.

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

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 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.

- **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 \geq 65 years).
- **Renal Impairment:** Mild to moderate renal impairment ($CL_{cr} \geq 30$ mL/min/1.73 m²) had no influence on plasma concentrations of rosuvastatin. However, plasma concentrations of rosuvastatin increased to a clinically significant extent (about 3-fold) in patients with severe renal impairment ($CL_{cr} < 30$ mL/min/1.73 m²) not receiving hemodialysis compared with healthy subjects ($CL_{cr} > 80$ mL/min/1.73 m²).
- **Hemodialysis:** Steady-state plasma concentrations of rosuvastatin in patients on chronic hemodialysis were approximately 50% greater compared with healthy volunteer subjects with normal renal function.
- **Hepatic Impairment:** In patients with chronic alcohol liver disease, plasma concentrations of rosuvastatin were modestly increased.

In patients with Child-Pugh A disease, C_{\max} and AUC were increased by 60% and 5%, respectively, as compared with patients with normal liver function. In patients with Child-Pugh B disease,

C_{max} and AUC were increased 100% and 21%, respectively, compared with patients with normal liver function.

Drug-Drug Interactions:

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 Administered simultaneously Administered 2 hours apart	40 mg	↓ 54% [†]	↓ 50% [†]
	40 mg	↓ 22%	↓ 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	↑ 39%	↑ 36%
	80 mg	↑ 28%	↑ 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)]

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% S-Warfarin ↑6%	R-Warfarin ↓ 1% S-Warfarin 0%
40 mg QD for 12 days	Digoxin 0.5 mg single dose	↑ 4%	↑ 4%
40 mg QD for 28 days	Oral Contraceptive (ethinyl estradiol 0.035 mg & norgestrel 0.180, 0.215 and 0.250 mg) QD for 21 Days	EE ↑ 26% NG ↑ 34%	EE ↑ 25% NG ↑ 23%

EE = ethinyl estradiol, NG = norgestrel

*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.

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

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

Rosuvastatin was not teratogenic in rats at ≤ 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.

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.

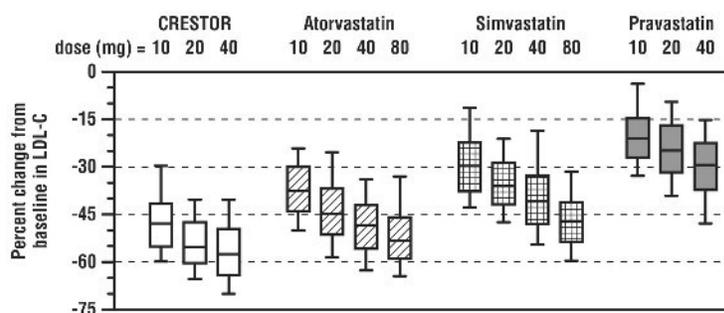
Dose-Ranging Study: In a multicenter, double-blind, placebo-controlled, dose-ranging study in patients with hyperlipidemia CRESTOR given as a single daily dose for 6 weeks significantly reduced Total-C, LDL-C, nonHDL-C, and ApoB, across the dose range (Table 6).

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).

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



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

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

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

* 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.

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

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

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 $\epsilon 2/\epsilon 2$ and 4 with apo E mutation [Arg145Cys] with primary dysbetalipoproteinemia (Type III Hyperlipoproteinemia) entered a 6-week dietary lead-in period on the NCEP Therapeutic Lifestyle Change (TLC) diet. Following dietary lead-in, patients were randomized to a sequence of treatments in conjunction with the TLC diet for 6 weeks each: rosuvastatin 10 mg followed by rosuvastatin 20 mg or rosuvastatin 20 mg followed by rosuvastatin 10 mg. CRESTOR reduced nonHDL-C (primary end point) and circulating remnant lipoprotein levels. Results are shown in the table below.

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

	Median at Baseline (mg/dL)	Median percent change from baseline (95 % CI) CRESTOR 10 mg	Median percent change from baseline (95% CI) CRESTOR 20 mg
Total-C	342.5	-43.3 (-46.9,-37.5)	-47.6 (-51.6,-42.8)
Triglycerides	503.5	-40.1 (-44.9, -33.6)	-43.0 (-52.5, -33.1)
NonHDL-C	294.5	-48.2 (-56.7, -45.6)	-56.4 (-61.4, -48.5)
VLDL-C + IDL-C	209.5	-46.8 (-53.7, -39.4)	-56.2 (-67.7, -43.7)
LDL-C	112.5	-54.4 (-59.1, -47.3)	-57.3 (-59.4, -52.1)
HDL-C	35.5	10.2	11.2

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

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.

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

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

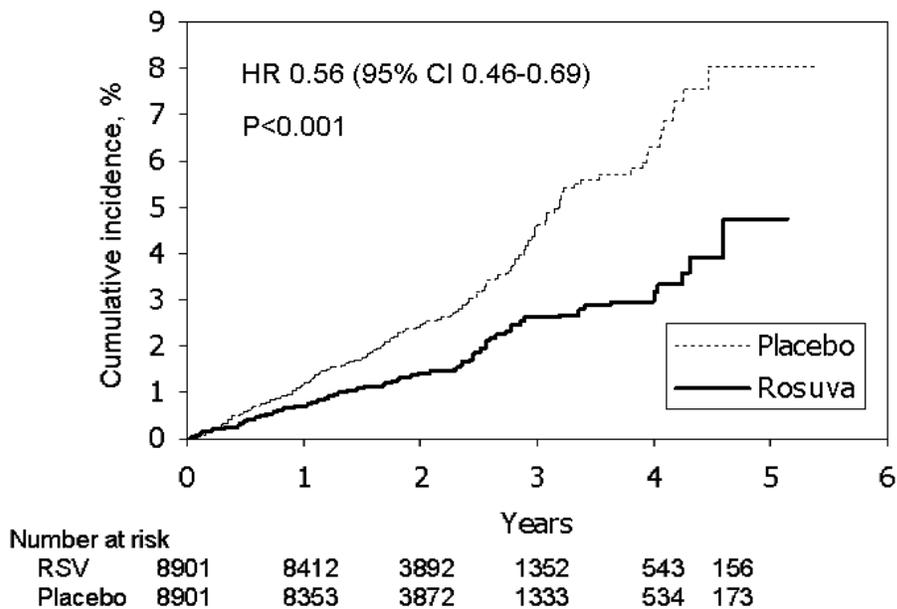
In the **Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER)** study, the effect of CRESTOR (rosuvastatin calcium) on the occurrence of major cardiovascular (CV) disease events was assessed in 17,802 men (≥ 50 years) and women (≥ 60 years)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

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

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

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

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

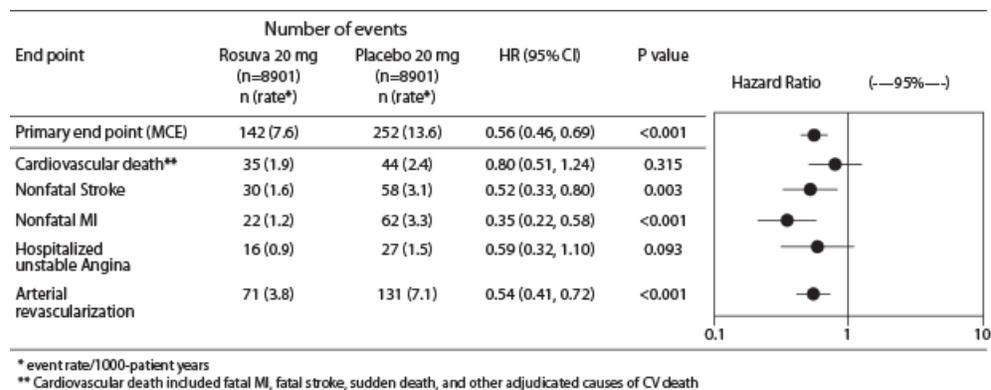


The individual components of the primary end point are presented in Figure 3. Rosuvastatin significantly reduced the risk of nonfatal myocardial infarction, nonfatal stroke, and arterial revascularization procedures. There were no significant treatment differences between the rosuvastatin and placebo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

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

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

Figure 3. Major CV events by treatment group in JUPITER



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

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, 20-25°C (68-77°F) [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.

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

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ASTRAZENECA

Rev. Month, 2012

PATIENT INFORMATION

CRESTOR[®] (rosuvastatin calcium) Tablets
(Kres-tor)

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

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

What is CRESTOR?

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

What is Cholesterol?

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

Common health factors such as diabetes, high blood pressure, smoking, obesity, family history of early heart

disease, and age can make controlling your cholesterol even more important.

What is Atherosclerosis?

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

How Does CRESTOR Work?

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

Who Should Not Take CRESTOR?

Do not take CRESTOR if you:

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

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

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

Tell your health care professional if you:

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

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

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

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

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

How Should I Take CRESTOR?

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

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

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

Swallow the tablets whole.

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

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

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

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

What Should I Avoid While Taking CRESTOR?

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

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

What are the Possible Side Effects of CRESTOR?

CRESTOR can cause side effects in some people.

Serious side effects may include:

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

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

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

The most common side effects may include:

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

The following additional side effects have been reported with CRESTOR:

Memory loss and confusion

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

How Do I Store CRESTOR?

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

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

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

What are the Ingredients in CRESTOR?

Active Ingredient: rosuvastatin as rosuvastatin calcium

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

General Information About CRESTOR

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

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

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ASTRAZENECA

Rev. Month, 2012

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/s/

AMY G EGAN
02/28/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
021366Orig1s024

Tracked Changes Label

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)	10/2009
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 enzymes tests before initiating therapy and during treatment as clinically indicated thereafter. (5.2)

ADVERSE REACTIONS

Most frequent adverse reactions (rate $\geq 2\%$) 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 increase 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 POPULATIONS

- 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).

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.

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

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 fenofibrate¹⁰; 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 m²) not on hemodialysis, dosing of CRESTOR should be started at 5 mg once daily and not exceed 10 mg once daily [*see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

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 \geq 65 years, inadequately treated hypothyroidism, renal impairment).

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

CRESTOR therapy should be discontinued if markedly elevated 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

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

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 $\geq 2\%$) in the CRESTOR controlled clinical trial database of 5394 patients were:

- headache
- myalgia
- abdominal pain

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

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

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

* 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.

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

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

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

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

* 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

(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 $\geq 2\%$ of patients and at a rate greater than placebo are shown in Table 3.

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

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

* 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.

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)].

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)*].

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

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

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 m²); however, exposure to rosuvastatin is increased to a clinically significant extent in patients with severe renal impairment who are —not receiving hemodialysis. CRESTOR dosing should be adjusted in patients with severe renal impairment ($CL_{cr} < 30$ mL/min/1.73 m²) not requiring hemodialysis [*see Dosage and Administration* (2.7), *Warnings and Precautions* (5.1) and *Clinical Pharmacology* (12.3)].

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)*].

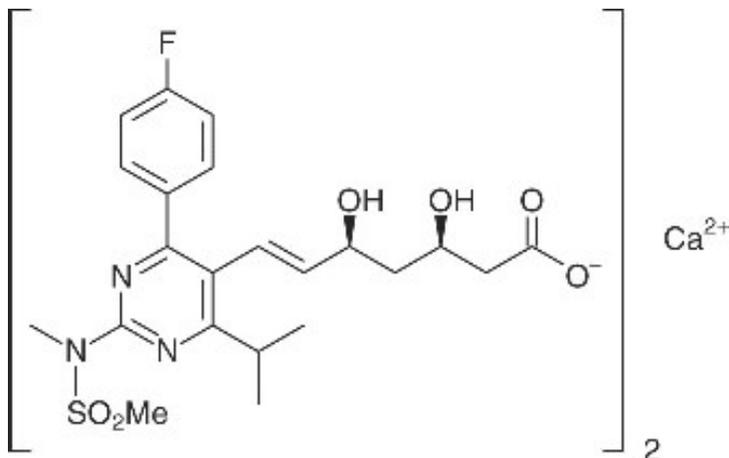
10 OVERDOSAGE

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:



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

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

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

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.

- **Race:** A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic, and Black or Afro-Caribbean groups. However, pharmacokinetic studies, including one conducted in the US, have demonstrated an approximate 2-fold elevation in median exposure (AUC and C_{\max}) in Asian subjects when compared with a Caucasian control group.
- **Gender:** There were no differences in plasma concentrations of rosuvastatin between men and women.
- **Geriatric:** There were no differences in plasma concentrations of rosuvastatin between the nonelderly and elderly populations (age ≥ 65 years).
- **Renal Impairment:** Mild to moderate renal impairment ($CL_{cr} \geq 30$ mL/min/1.73 m²) had no influence on plasma concentrations of rosuvastatin. However, plasma concentrations of rosuvastatin increased to a clinically significant extent (about 3-fold) in patients with severe renal impairment ($CL_{cr} < 30$ mL/min/1.73 m²) not receiving hemodialysis compared with healthy subjects ($CL_{cr} > 80$ mL/min/1.73 m²).
- **Hemodialysis:** Steady-state plasma concentrations of rosuvastatin in patients on chronic hemodialysis were approximately 50% greater compared with healthy volunteer subjects with normal renal function.
- **Hepatic Impairment:** In patients with chronic alcohol liver disease, plasma concentrations of rosuvastatin were modestly increased.

In patients with Child-Pugh A disease, C_{\max} and AUC were increased by 60% and 5%, respectively, as compared with patients with normal liver function. In patients with Child-Pugh B disease, C_{\max} and AUC were increased 100% and 21%, respectively, compared with patients with normal liver function.

Drug-Drug Interactions:

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			
Administered simultaneously	40 mg	↓ 54% [†]	↓ 50% [†]
Administered 2 hours apart	40 mg	↓ 22%	↓ 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	↑ 39%	↑ 36%
	80 mg	↑ 28%	↑ 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)]

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% S-Warfarin ↑6%	R-Warfarin ↓ 1% S-Warfarin 0%
40 mg QD for 12 days	Digoxin 0.5 mg single dose	↑ 4%	↑ 4%
40 mg QD for 28 days	Oral Contraceptive (ethinyl estradiol 0.035 mg & norgestrel 0.180, 0.215 and 0.250 mg) QD for 21 Days	EE ↑ 26% NG ↑ 34%	EE ↑ 25% NG ↑ 23%

EE = ethinyl estradiol, NG = norgestrel

*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.

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

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

Rosuvastatin was not teratogenic in rats at ≤ 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.

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.

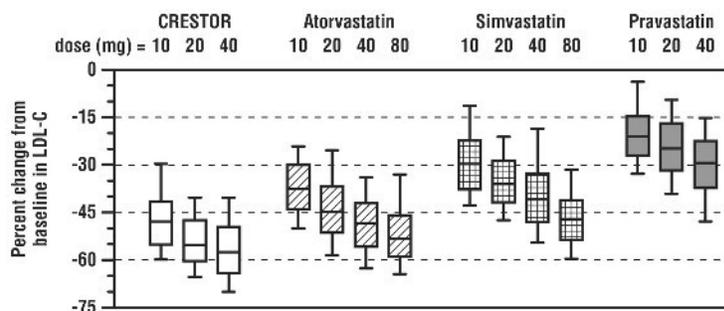
Dose-Ranging Study: In a multicenter, double-blind, placebo-controlled, dose-ranging study in patients with hyperlipidemia CRESTOR given as a single daily dose for 6 weeks significantly reduced Total-C, LDL-C, nonHDL-C, and ApoB, across the dose range (Table 6).

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).

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



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

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

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

* 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.

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

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

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 $\epsilon 2/\epsilon 2$ and 4 with apo E mutation [Arg145Cys] with primary dysbetalipoproteinemia (Type III Hyperlipoproteinemia) entered a 6-week dietary lead-in period on the NCEP Therapeutic Lifestyle Change (TLC) diet. Following dietary lead-in, patients were randomized to a sequence of treatments in conjunction with the TLC diet for 6 weeks each: rosuvastatin 10 mg followed by rosuvastatin 20 mg or rosuvastatin 20 mg followed by rosuvastatin 10 mg. CRESTOR reduced nonHDL-C (primary end point) and circulating remnant lipoprotein levels. Results are shown in the table below.

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

	Median at Baseline (mg/dL)	Median percent change from baseline (95 % CI) CRESTOR 10 mg	Median percent change from baseline (95% CI) CRESTOR 20 mg
Total-C	342.5	-43.3 (-46.9,-37.5)	-47.6 (-51.6,-42.8)
Triglycerides	503.5	-40.1 (-44.9, -33.6)	-43.0 (-52.5, -33.1)
NonHDL-C	294.5	-48.2 (-56.7, -45.6)	-56.4 (-61.4, -48.5)
VLDL-C + IDL-C	209.5	-46.8 (-53.7, -39.4)	-56.2 (-67.7, -43.7)
LDL-C	112.5	-54.4 (-59.1, -47.3)	-57.3 (-59.4, -52.1)
HDL-C	35.5	10.2	11.2

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

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.

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

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

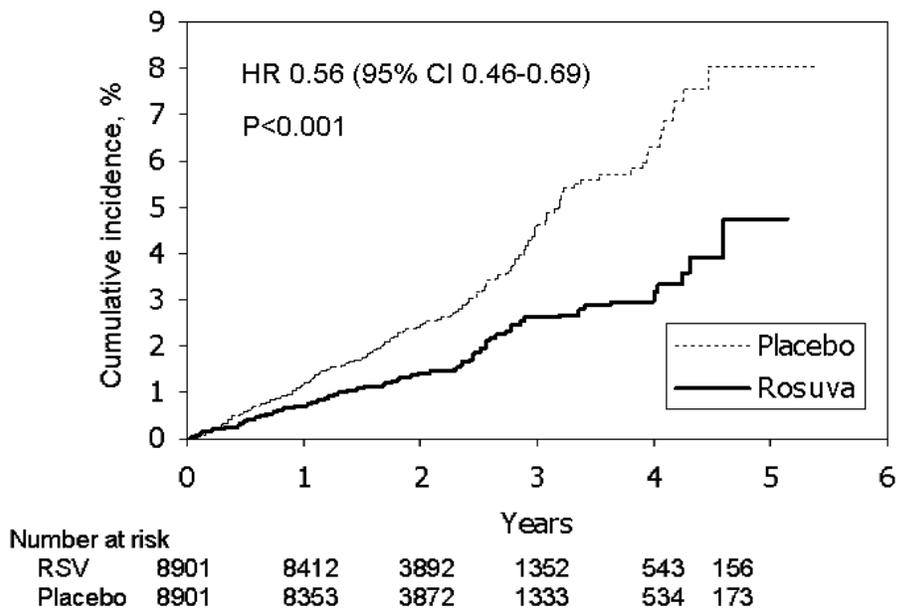
In the **Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER)** study, the effect of CRESTOR (rosuvastatin calcium) on the occurrence of major cardiovascular (CV) disease events was assessed in 17,802 men (≥ 50 years) and women (≥ 60 years)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

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

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

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

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

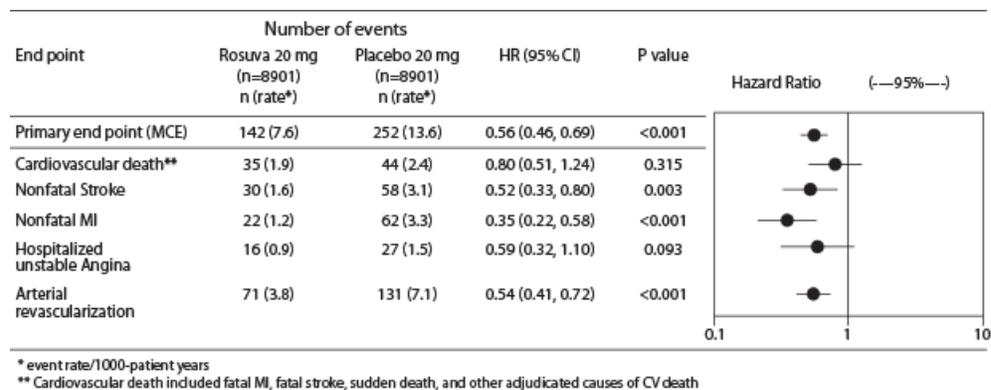


The individual components of the primary end point are presented in Figure 3. Rosuvastatin significantly reduced the risk of nonfatal myocardial infarction, nonfatal stroke, and arterial revascularization procedures. There were no significant treatment differences between the rosuvastatin and placebo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

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

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

Figure 3. Major CV events –by treatment group in JUPITER



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

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, 20-25°C (68-77°F) [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.

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 enzymes 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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PATIENT INFORMATION

CRESTOR[®] (rosuvastatin calcium) Tablets
(Kres-tor)

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

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

What is CRESTOR?

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

What is Cholesterol?

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

Common health factors such as diabetes, high blood pressure, smoking, obesity, family history of early heart

disease, and age can make controlling your cholesterol even more important.

What is Atherosclerosis?

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

How Does CRESTOR Work?

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

Who Should Not Take CRESTOR?

Do not take CRESTOR if you:

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

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

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

Tell your health care professional if you:

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

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

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

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

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

How Should I Take CRESTOR?

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

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

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

Swallow the tablets whole.

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

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

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

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

What Should I Avoid While Taking CRESTOR?

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

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

What are the Possible Side Effects of CRESTOR?

CRESTOR can cause side effects in some people.

Serious side effects may include:

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

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

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

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

The following additional side effects have been reported with CRESTOR:

Memory loss and confusion

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

How Do I Store CRESTOR?

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

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

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

What are the Ingredients in CRESTOR?

Active Ingredient: rosuvastatin as rosuvastatin calcium

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

General Information About CRESTOR

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

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

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
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MEDICAL REVIEW(S)

Clinical Review for Statin Class Labeling Changes

February 15, 2012

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On August 11, 2011 the Division of Metabolism and Endocrinology Products (DMEP) issued supplement request letters to the sponsors of all HMG-CoA reductase inhibitor (statin) drugs requesting changes to the labeling so as to furnish adequate information for the safe and effective use of their statin. These labeling changes were based on FDA's comprehensive review of the statin class of drugs, including clinical trial data, Adverse Event Reporting System (AERS) reports, the published literature, and the labels of other approved drugs containing information on statin co-administration. This review will serve to summarize the safety issues and the sources and reviews of the data.

1. Liver enzyme abnormalities – TSI #57

On March 19, 2007 DMEP opened Tracked Safety Issue (TSI) #57 to evaluate hepatotoxicity associated with the statin class of drugs. This was based on articles in the published literature which suggested that FDA should re-evaluate current recommendations in statin labeling for routine periodic monitoring of liver enzyme tests.

In March 2008, DMEP issued Information Request letters to the statin sponsors requesting the following:

- a. Does <<APPLICANT>> have an opinion or recommendation regarding the utility of baseline and/or periodic monitoring of serum aminotransferase activity prior to and/or during treatment with <<STATIN>>? Please address this question for subjects with normal liver function and for those with asymptomatic liver disease (e.g., NAFLD, hepatitis C).
- b. Upon what clinical evidence or other consideration are these opinions or recommendations based?
- c. Please provide the number of phase 2 and 3 trials conducted with <<STATIN>> for which you have access to the raw data.

The table below summarizes the sponsors' responses to the first question:

Table 10. Overview of Industry responses to FDA questions on hepatotoxicity of statins			
Sponsor	Product	Text suggests interest in withdrawal of monitoring	caveats
Andrx	Lovastatin ER	No	none
AstraZeneca	rosuvastatin	Yes	none
Bristol-Myers Squibb	pravastatin	N/A	No text to delete
Merck	lovastatin	No	None
Merck	simvastatin	No	None
Novartis	fluvastatin	No	None
Pfizer	atorvastatin	Yes	10 mg dose only

In general, most sponsors agreed that liver enzyme testing prior to initiation of statin therapy was appropriate, but acknowledged that there appeared to be limited utility to routine liver biochemistry monitoring during treatment. One sponsor commented on the recommendations of the Liver Expert Panel convened by the National Lipid Association which stated that “because there is no evidence that a relation exists between elevated serum aminotransferase levels and significant liver injury, or that routine monitoring of liver biochemistries will identify individuals likely to develop rare cases of idiosyncratic liver failure, the requirement for routine liver biochemistry monitoring in patients receiving any of the currently marketed statin therapies should be re-examined.” Another sponsor noted that “nearly 50% of hyperlipidemic patients have coexisting non-alcoholic fatty liver disease (NAFLD) and it is well known that LFT levels fluctuate in NAFLD.”

In conjunction with the request to statin sponsors, DMEP requested that the Office of Surveillance and Epidemiology (OSE) conduct a review to characterize the risk of clinically serious hepatotoxicity in association with statins and assist in a determination if the statin class labeling for liver enzyme monitoring should be retained, revised, or removed. OSE had conducted 5 postmarket reviews of statins and hepatotoxicity between 2000 and 2009. Those reviews had consistently noted that reporting of statin-associated serious liver injury to AERS was extremely low (reporting rate of ≤ 2 per one million patient-years).

The OSE review of AERS was completed May 13, 2011. The review focused on cases of severe liver injury, defined as a 4 (severe liver injury) or a 5 (death or liver transplant) using the Drug Induced Liver Injury Network (DILIN) liver injury severity scale. Cases meeting those criteria were further assessed for causality. Seventy-five cases (27 with a severity score of 4 and 48 with a severity score of 5 [37 deaths and 11 liver transplants]) were assessed for causality, 30 of which (14 deaths, 7 liver transplantations, and 9 severe liver injury) were assessed as possibly (25-49% likelihood) or probably (50-74% likelihood) associated with

statin therapy. No cases were assessed as highly likely (75-95% likelihood) or definitely (>95% likelihood) associated with statin therapy. OSE noted that “despite rising use of statins as a class since the late 1990s, there has not been a detectable uptick in the annual rates of fatal (deaths or liver transplant) or severe liver injury possibly or probably causally associated cases.” The cases are summarized in the table below:

Liver Injury Severity Score	5 (Death)	5 (Transplant)	4 (Severe)
# of Cases	14	7	9
Median Age in Years (range)	66 (51-89)	48 (40-71)	58 (47-71)
Percent Female	79% (11/14)	71% (5/7)	67% (6/9)
Statin at the Time of Event Median Daily Dose in mg (range [n])			
Atorvastatin	4 -- (10, 10 [n=2])	3 10 (10-20 [n=3])	4 10 (10-20 [n=3])
Cerivastatin	--	--	--
Fluvastatin	--	--	1 -- (20 [n=1])
Lovastatin	1 -- (20 [n=1])	1 -- (-- [n=0])	--
Pravastatin	3 -- (20, 40 [n=2])	--	1 -- (10 [n=1])
Rosuvastatin	--	--	--
Simvastatin	6 20 (10-40 [n=5])	3 20 (20-40 [n=3])	3 -- (40 [n=1])
Time to Onset in Months**, Median (range)	2.5 (3 wk – 12 mo)	1.5 (2.4 wk - 6 mo)	2 (5 wk – 8 mo)
Peak Serum Total Bilirubin Level in mg/dL, Median (range [n])	23 (2.9-51 [n=12])	27 (22-32 [n=4])	10 (1.2-25 [n=9])
Peak Serum ALT Level in units/L, Median (range[n]) reference range: 6-41 units/L	1,127 (148-4,300 [n=10])	2,912 (2,037-13,531[n=4])	1,319 (538-3,000 [n=9])
Peak Serum AST Level in units/L, Median (range[n]) reference range: 9-34 units/L	1,497 (81-7,200 [n=11])	2,294 (1,755-6,815 [n=4])	1,260 (853-3,000 [n=9])
Peak Serum ALP Level in units/L, Median (range[n]) reference range: 37-116 units/L	206 (155-623 [n=9])	-- (290, 602 [n=2])	307 (131-800 [n=4])

*Defined as probably associated (supported by the evidence as implicating the drug but not definite or highly likely) or possibly associated (causality is not supported by the preponderance of evidence, but one cannot definitively exclude the possibility)

**Time to onset defined as the interval between exposure time or time after dose increased to reported liver injury event

OSE also looked at cases from the DILIN and Acute Liver Failure Study Group (ALFSG), organizations which have been systematically submitting reports to FDA of drug associated liver injury referred to their respective liver injury outcome studies. For statin associated liver injury, DILIN has submitted 25 reports to FDA as of January 1, 2011, twelve of which resulted in an outcome of hospitalization. In the ALFSG database, there were 9 reports of drug-induced liver injury (DILI) associated with statin therapy. OSE cited a 2010 article from

ALFSG that included 133 prospectively identified cases of idiopathic DILI resulting in acute liver failure. Fifteen patients were taking statins and in 6 of these 15 individuals a statin was identified as the only potential DILI agent. The authors noted that statin hepatotoxicity is “generally benign” and the identification of these 6 cases represents a “provocative observation”.

Using the AERS and drug utilization databases, reporting rates were calculated for U.S. statin cases associated with liver injury and an outcome of death or liver transplant, from the time of initial marketing approval through January 1, 2009. It should be noted that reporting rates are subject to secular reporting trends which normally preclude generation of reporting rates between products with initial marketing dates greater than 2-4 years apart. Despite the limitations of the analysis, it appears that reporting levels for serious liver injury in association with currently marketed statins are generally similar.

Table 9. Number of U.S. Statin Cases Associated with Liver Injury and an Outcome of Death or Liver Transplant (Severity Score 5). Initial Marketing Approval Through January 1, 2009

Generic Name (Brand)	Number of cases	Total Number of Prescriptions (TRxs) Dispensed by U.S. Retail Pharmacies, 1991-2008† (in millions)	Observed reporting rate as cases per (b) (4)
Lovastatin (Mevacor, Advicor, Altocor)	23		(b) (4)
Pravastatin (Pravachol)	11		(b) (4)
Simvastatin (Zocor, Vytorin, Simcor)	51		(b) (4)
Fluvastatin (Lescol)	4		(b) (4)
Atorvastatin (Lipitor)	64		(b) (4)
Rosuvastatin (Crestor)	3		(b) (4)
Total	156		(b) (4)

OSE also reviewed current monitoring guidelines including the National Lipid Association’s Liver Expert Panel, which state:

The Liver Expert Panel does not believe that the available scientific evidence supports the routine monitoring of liver biochemistries in asymptomatic patients receiving statins. The Panel makes this recommendation because (1) irreversible liver damage resulting from statins is exceptionally rare and is likely idiosyncratic in nature, and (2) no data exist to show that routine monitoring of liver biochemistries is effective in identifying the very rare individual who may develop significant liver injury from ongoing statin therapy. In the view of the Panel, routine monitoring will instead identify patients with isolated

increased aminotransferase levels, which could motivate physicians to alter or discontinue statin therapy, thereby placing patients at increased risk for cardiovascular events.

OSE further noted that the NLA's Statin Safety Task Force had a slightly divergent opinion and made the following recommendation:

Until there is a change in the FDA-approved prescribing information for statins, it is appropriate to continue to measure transaminase levels before starting therapy, 12 weeks after initiating therapy, after a dose increase, and periodically thereafter. However, routine monitoring of liver function tests is not supported by the available evidence and the current recommendation for monitoring needs to be reconsidered by the FDA.

The OSE review concluded:

Serious, hepatocellular DILI can be caused by statins. Although the routine monitoring of serum ALT and other markers for liver injury is vital for drug development, it does not appear to be useful in a post marketing, non study, ambulatory setting to routinely detect and prevent serious liver injury in association with statins. In place of current recommendations for serum enzyme monitoring, labeling for statins should focus on an alert to identify serious liver injury and clinical symptoms of liver injury, interruption of therapy, physician interactions, and emphasize the importance of appropriate diagnostic work up.

OSE further recommended:

It is justified that the recommendation to perform routine periodic serum ALT monitoring in all treated patients at prespecified intervals currently in place for some marketed statins be removed.

Based on these recommendations, DMEP requested the following changes to statin labeling:

Under HIGHLIGHTS OF PRESCRIBING INFORMATION, under **WARNINGS AND PRECAUTIONS**:

Liver enzyme abnormalities: Persistent elevations in hepatic transaminases can occur. Check liver enzyme tests before initiating therapy and as clinically indicated thereafter.

Under **5 WARNINGS AND PRECAUTIONS**, [REDACTED] (b) (4)

It is recommended that liver enzyme tests be performed before the initiation of <<STATIN>> [REDACTED] (b) (4)

There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including <<STATIN>>. If serious liver injury with clinical symptoms and/or

hyperbilirubinemia or jaundice occurs during treatment with <<STATIN>>, promptly interrupt therapy. If an alternate etiology is not found do not restart <<STATIN>>.

Under 6 ADVERSE REACTIONS, Post-Marketing Experience:

(b) (4)

Under 17 PATIENT COUNSELING INFORMATION, Liver Enzymes:

It is recommended that liver enzyme tests be (b) (4) before the initiation of <<STATIN>> and if signs or symptoms of liver injury occur. All patients treated with <<STATIN>> should be advised to report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice.

(b) (4)

2. Cognitive effects – TSI #772

On September 2, 2009 DMEP opened TSI #772 to evaluate the effect of statins on cognition. This was based on a complaint received from Joe Graedon of the People’s Pharmacy, and an unpublished study by Duane Graveline, M.D., M.P.H. and Jay S. Cohen, M.D. entitled “Lipitor-associated memory loss: analysis of 662 cases of cognitive damage”, as well as other articles from the published literature.

In attempting to assess this risk, DMEP looked initially at pre-clinical data. Several of the statin drug sponsors had performed pre-clinical cognition studies; however, those studies only address the issue of dementia syndromes, and are less helpful in addressing the issue of acute confusional states or memory impairment. Therefore, it was determined that there was no value added to re-assessing the pre-clinical data.

DMEP sent information request letters to those statin sponsors who had conducted clinical trials in which some form of neurocognitive assessment had been conducted as part of the study protocol. Those trials included: Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), Heart Protection Study (HPS), and Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH).

The findings were as follows:

- **PROSPER:** Subjects were screened with a Mini Mental Status Exam (MMSE) and excluded if their score was <24. Cognitive function was assessed in all 5,804 participants at six different time points during the study.

Four neuropsychological tests were performed, two of which tested executive function (attention and speed) and two of which tested memory (immediate and delayed). All tests showed a significant decline over time (3-year follow-up); however, there was no difference between treatment groups, pravastatin 40 mg versus placebo.

- **HPS:** A modified Telephone Interview for Cognitive Status (TICS-m) questionnaire was administered to participants during their final follow-up, either face-to-face in the clinic or over the telephone. Data were available on 8086/10269 (79%) of simvastatin-allocated subjects and 7834/10267 (76%) of placebo-allocated subjects. No significant differences were observed between the treatment groups in the percentages of participants classified as cognitively impaired (defined as a TICS-m score below 22 out of 39), either overall (23.7% simvastatin 40 mg-allocated vs. 24.2% placebo-allocated) or in subgroups defined with respect to their age at study entry (<65 years: 17.1% vs. 17.8%; 65-69 years: 25.8% vs. 25.4%; 70-80 years: 34.6% vs. 36.2%) or their previous history of cerebrovascular disease (no prior stroke: 22.8% vs. 23.3%; prior stroke: 31.9% vs. 33.3%). Nor was there any significant difference between the groups in mean TICS-m score (24.08 vs. 24.06). Similar numbers of participants in each treatment group were reported to have developed dementia during follow-up (31 [0.3%] vs. 31 [0.3%]).

There was a slightly higher frequency of cases of Alzheimer's disease or Alzheimer's type dementia in patients on simvastatin (n=6) compared to placebo (n=3). When looking at all patients with potential diagnoses of dementia including Alzheimer's disease, confusion, disorientation, dementia or cognitive impairment, there was no difference in the frequency of patients in the simvastatin group (n=35; 0.34%) compared to placebo (n=33; 0.32%).

- **SEARCH:** Assessment of cognitive function, using the TICS-m score, was a tertiary endpoint for the folate arm of the trial. It was performed in 8891 subjects – 4473 on simvastatin 80 mg and 4418 on simvastatin 20 mg – at the final visit. There was no difference in mean TICS-m score between treatment groups (24.3 ± 4.1 for simvastatin 80 mg vs. 24.3 ± 4.3 for simvastatin 20 mg), and no difference in percentages of patients with scores <20, ≥ 20 , <22, ≥ 22 , <25, ≥ 25 , <30, ≥ 30 between treatment groups. The TICS-m score reflects memorizing ability in large part. Verbal fluency scores also did not differ among patients allocated to simvastatin 80 mg and simvastatin 20 mg. Hearing thresholds were assessed at final follow-up and did not differ between the simvastatin groups.

The incidence of memory loss attributed to study treatment was 17 (0.3%) in patients allocated to simvastatin 80 mg, and 8 (0.1%) in patients allocated to simvastatin 20 mg.

It should also be noted that while no formal neurocognitive assessment was performed in the Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), there was noted a

statistically significant increase in the reported adverse event of confusional state in subjects allocated to rosuvastatin 20 mg (n=8 [0.2%]) versus subjects allocated to placebo (n=4 [0.04%]).

DMEP was aware of a Phase III efficacy study of atorvastatin that had been conducted in patients with mild to moderate Alzheimer's Disease. The clinical study report for this study (Study A2581078) was requested from the sponsor and consulted to the Division of Neurology Products (DNP) for review. DNP's findings were as follows:

The results of Study A2581078, an adequately-designed Phase III efficacy and safety study of atorvastatin (Lipitor) in patients with mild to moderate Probable Alzheimer's Disease, provide no evidence that the administration of Lipitor results in cognitive worsening in this population; neither was there any evidence of a worsening of global function in those treated with atorvastatin in this study.

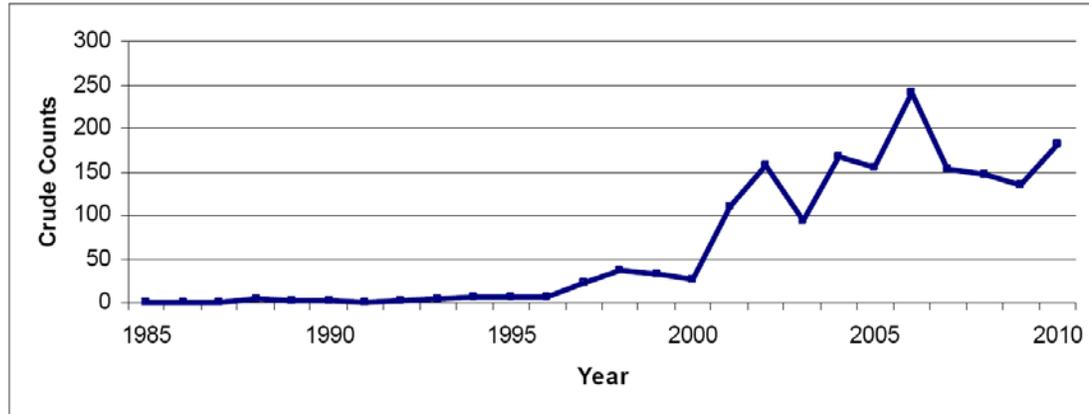
DMEP consulted OSE and requested that a review of AERS and the published literature be conducted to further assess the effect of statins on cognition. In 2002, OSE had performed a review of 279 statin reports associated with transient memory loss. This review had been requested by DMEP in response to a consumer report of transient global amnesia (TGA) with atorvastatin. At that time, OSE determined that the calculated reporting rate for statin-associated TGA (0.12-0.55 per 100,000 patient years) was well below the background incidence rate (3.4-32/100,000 population per year). As memory loss was already included in the statin labels, no labeling change was recommended at that time.

OSE's updated review of AERS focused on reports of serious cases of memory impairment, using the following High Level Terms (HLT):

- Mental Impairment (excluding dementia and memory loss)
- Memory Loss (excluding dementia)
- Amnestic Symptoms
- Confusion and Disorientation

Through January 1, 2011 there were 1,698 U.S. serious reports (crude counts) in AERS.

Figure 1. Number of U.S. Serious Statin* Reports (Crude Counts) Associated with Cognitive Change†, by Year Received. Source: AERS, Initial Marketing Approval Through January 1, 2011 (n=1,698)



*Includes single ingredient and combination statin products approved by FDA.

†Reports identified in AERS using four HLTs: Mental Impairment (excluding dementia & memory loss), Memory Loss (excluding dementia), Amnesic Symptoms, and Confusion and Disorientation

Further case review was limited to 182 reports received by FDA in 2010. Of those reports, 57 unique cases described transient cognitive change as the primary adverse event. Sixty nine percent (n=125) of the cases were excluded because they reported multiple events such as rhabdomyolysis, renal failure, and confusion (n=81), were duplicates (n=18), hearsay (n=3), reported by attorneys (n=5), or solicited reports (n=16).

Characteristics of the 57 cases included:

- Age: median of 62 years (30-85)
- Sex: 62% male
- Exposure time: median of 3 years (1 month-12 years)

The literature review included case series of transient cognitive impairment associated with statin use, as well as observational studies on the association between statin use and the incidence of dementia. The observational evidence was summarized based on a meta-analysis by Zhou and colleagues:

After conducting a systematic review, the authors identified four cohort studies and three case-control studies which examined the association between statin use and dementia. The average observation period ranged from three to nine years. Three case-control studies suggested statin use may lower the incidence of dementia; while the remaining four cohort studies failed to demonstrate an association between statin use and incident dementia. A pooled analysis also failed to demonstrate an association between statin use and incident dementia.

OSE further noted:

Results from three prospective cohort studies published within the last year provide similar conflicting results. Analyses of Baltimore Longitudinal Study of Aging and the Ginkgo Evaluation of Memory Study suggested that statin use is associated with a lower risk of dementia. A nested case control study in the Neurological Disorders in Central Spain cohort failed to detect an association between statin use and cross sectional performance on a neuropsychological test battery.

Table 5. Observational Studies Summary: Statin Use and Cognition				
Author (Publication Date)	Study Design	Total Sample Size (% Exposed to Statins)	Outcome	Key Result
Zhou (2007)	Meta-Analysis – Observational Studies	10523 (12%)	Incident Dementia	Adjusted OR=0.77 (95%: 0.45-1.30)
Beydoun (2010)	Cohort Study	1604 (7%)	Incident Dementia	Adjusted HR=0.21 (95%: 0.09-0.48)
Betterman (2011)	Cohort Study	3069 (25%)	Incident Dementia	Adjusted HR=0.79 (95%: 0.65-0.96)
Benito-Leon (2010)	Nested Case-Control	548 (25%)	Neuropsychological Test Performance	No treatment effect observed in any test neuropsychological test administered (global cognition, verbal fluency, psychomotor speed, confrontational naming, verbal memory, logical memory)

OSE concluded:

The postmarket statin reports associated with transient cognitive change generally describe individuals over the age of 50 years who experience notable (sometimes described as “dramatic”), but ill defined memory loss or impairment (e.g., “lost my mind”) that is reversible upon discontinuation of statin therapy. The statin exposure time to onset of the event is highly variable (1 day to years). These cases do not appear to be associated with fixed or progressive dementia, such as Alzheimer’s disease.

Like the previous (2002) OSE review, the analyzed data in this review did not reveal any discernible dose event or age (the reported age at the time of event is similar to the age of the population using statins) trends or effects between statins and other drugs; few reports described neurologic follow-up or standardized testing results. Findings from this review (and the 2002 OSE review) are also similar to patient survey results recently published by the University of California San Diego (UCSD) Statin Effects Study investigators. Cognitive issues were reported for all statins, with atorvastatin and simvastatin most frequently reported. The time to onset was variable (1 day to 10 years). Ninety percent reported symptom improvement after the statin was discontinued. Complete recovery time varied from 1 day to several years (median time to first noted improvement was 2.5 weeks). Of 29 participants who underwent rechallenge, 19 reported recurrence of events.

An analysis of the epidemiologic evidence and clinical trials did not provide evidence that chronic statin use is associated with cognitive decline at the population level. Two studies demonstrated that exposure to statins for up to six months may prevent the acquisition of a practice effect on select neuropsychological measures. However, the clinical significance of an absent practice effect in the context of normal cognitive performance is questionable. Furthermore, no study systematically assessed patients who experienced statin associated cognitive impairment during both dechallenge and rechallenge. Such systematic studies would provide additional evidence to support a causal association and better characterize the clinical phenotype.

OSE recommended that DMEP consider statin class labeling that would characterize the nature of the cognitive changes. In response, DMEP requested that the following be added to the **Adverse Reactions, Postmarketing Experience** sub-section of all statin labels:

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).

(b) (4)

3. Drug-drug interaction with protease inhibitors – TSI #756

On July 23, 2009 TSI #756 was opened to examine the drug-drug interaction between statins and protease inhibitors.

In July 2009, the sponsor for rosuvastatin (CRESTOR) submitted a prior approval supplement (PAS) proposing to include information on increased rosuvastatin exposure when CRESTOR was co-administered with the combinations of protease inhibitors tipranavir/ritonavir, atazanavir/ritonavir or fosamprenavir/ritonavir, based on studies in the published literature. Previous CRESTOR labeling had noted a DDI with lopinavir/ritonavir (KALETRA) resulting in a dose cap of 10 mg of CRESTOR when co-administered with KALETRA.

In a January 2010 review of the PAS, it was noted that there were inconsistencies between the statin labels and the protease inhibitor labels regarding recommendations for co-administration of these products. It was therefore determined that the Office of Clinical Pharmacology (OCP) would review the relevant data on DDIs between statins and HIV and HCV protease inhibitors.

On August 3, 2011 OCP completed its review of the cross labeling initiative for drug interaction updates between protease inhibitors and statins. DMEP was requested to make changes to the atorvastatin and pravastatin labels to provide the results of DDI studies conducted with certain protease inhibitors, and in the case of atorvastatin, to provide dose caps where appropriate, based on the results of the following DDI studies:

- Tipranavir/ritonavir increases atorvastatin AUC and C_{max} 9.4-fold and 8.6-fold, respectively. Because clinical data demonstrating an increased risk of myopathy or rhabdomyolysis with co-administration are lacking, a contraindication was not supported and “Avoid atorvastatin” was recommended for labeling.
- Telaprevir increases atorvastatin AUC and C_{max} 7.88-fold and 10.6-fold, respectively. Because clinical data demonstrating an increased risk of myopathy or rhabdomyolysis with co-administration are lacking, a contraindication was not supported and “Avoid atorvastatin” was recommended for labeling.
- Darunavir/ritonavir increases atorvastatin AUC and C_{max} 3.4-fold and 2.25-fold, respectively. A dose cap of atorvastatin 20 mg was recommended for labeling.
- Fosamprenavir increases atorvastatin AUC and C_{max} 2.3-fold and 4.04-fold, respectively. A dose cap of atorvastatin 20 mg was recommended for labeling.

(b) (4)

Based on OCP's recommendation, DMEP requested the following changes to the atorvastatin and pravastatin labels:

Atorvastatin:

Under HIGHLIGHTS OF PRESCRIBING INFORMATION, **DRUG INTERACTIONS**, Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis (2.6, 5.1, 7, 12.3)	
Interacting Agents	Prescribing Recommendations
Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	Do not exceed 10 mg atorvastatin daily Avoid atorvastatin
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (ritonavir plus saquinavir plus ritonavir, lopinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir)	Caution when exceeding doses >20mg atorvastatin daily. The lowest dose necessary should be used. Do not exceed 20 mg atorvastatin daily
HIV protease inhibitor (nelfinavir)	Do not exceed 40 mg atorvastatin daily

Under **DOSAGE AND ADMINISTRATION**:

2.6 Dosage in Patients Taking Cyclosporine, Clarithromycin, Itraconazole, or Certain Protease Inhibitors a Combination of Ritonavir plus Saquinavir or Lopinavir plus Ritonavir

In patients taking cyclosporine or the HIV protease inhibitors (tipranavir plus ritonavir) or the Hepatitis C protease inhibitor (telaprevir), therapy ~~should be limited to with LIPITOR 40 mg once daily~~ should be avoided. In patients with HIV taking lopinavir plus ritonavir, caution should be used when prescribing LIPITOR and the lowest dose necessary employed. In patients taking clarithromycin, itraconazole, or in patients with HIV taking a combination of ~~ritonavir plus saquinavir plus ritonavir, or lopinavir plus ritonavir~~ darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir ~~for doses of therapy with~~ LIPITOR should be limited to exceeding 20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of LIPITOR is employed. In patients with HIV taking nelfinavir, therapy with LIPITOR should be limited to 40 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of LIPITOR is employed.

Under **5 WARNINGS AND PRECAUTIONS, 5.1 Skeletal Muscle**:

The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, clarithromycin, the hepatitis C protease inhibitor telaprevir, combinations of HIV protease inhibitors, including ritonavir plus saquinavir plus ritonavir, or lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, niacin, or azole antifungals. Physicians considering combined therapy with LIPITOR and fibric acid derivatives, erythromycin, clarithromycin, a combination of ritonavir plus saquinavir plus ritonavir, or lopinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, immunosuppressive drugs, azole antifungals, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug.

Under Table 1. Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis:

Table 1. Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Cyclosporine, <u>HIV protease inhibitors (tipranavir plus ritonavir)</u> , hepatitis C protease inhibitor (<u>telaprevir</u>)	<u>Do not exceed 10 mg atorvastatin daily</u> <u>Avoid atorvastatin</u>
<u>HIV protease inhibitor (lopinavir plus ritonavir)</u>	<u>Use with caution and lowest dose necessary</u>
Clarithromycin, itraconazole, HIV protease inhibitors (<u>ritonavir plus saquinavir plus ritonavir*</u> , or <u>lopinavir plus ritonavir</u> , <u>darunavir plus ritonavir</u> , <u>fosamprenavir</u> , <u>fosamprenavir plus ritonavir</u>)	<u>Caution when exceeding doses >20mg atorvastatin daily. The lowest dose necessary should be used.</u> <u>Do not exceed 20 mg atorvastatin daily</u>
<u>HIV protease inhibitor (nelfinavir)</u>	<u>Do not exceed 40 mg atorvastatin daily</u>

*Use with caution and with the lowest dose necessary

Under DRUG INTERACTIONS, Combination of Protease Inhibitors, 7.1 Strong Inhibitors of CYP 3A4:

Combination of Protease Inhibitors: Atorvastatin AUC was significantly increased with concomitant administration of LIPITOR 40 mg with several combinations of HIV protease inhibitors, as well as with the Hepatitis C protease inhibitor telaprevir, ritonavir plus saquinavir (400 mg twice daily) or LIPITOR 20 mg with lopinavir plus ritonavir (400 mg + 100 mg twice daily) compared to that of LIPITOR alone [see *Clinical Pharmacology* (12.3)]. Therefore, in patients taking the HIV protease inhibitors tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir, concomitant use of LIPITOR should be avoided. In patients taking the HIV protease inhibitor lopinavir plus ritonavir, caution should be used when prescribing LIPITOR and the lowest dose necessary should be used. In patients taking the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, the

dose of LIPITOR should not exceed 20 mg and should be used with caution. ~~caution should be used when the LIPITOR dose exceeds 20 mg.~~

Under 12 CLINICAL PHARMACOLOGY, 12.3 Pharmacokinetics, TABLE 3. Effect of Coadministered Drugs on the Pharmacokinetics of Atorvastatin:

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC	Change in Cmax
Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	10 mg, SD	↑9.4 fold	↑8.6 fold
Nelfinavir 1250 mg BID, 14 days	10 mg QD for 28 days	↑74%	↑2.2-fold
Fosamprenavir 1400 mg BID, 14 days	10 mg QD for 4 days	↑2.3-fold	↑4.04-fold
Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	10 mg QD for 4 days	↑2.53-fold	↑2.84-fold
Darunavir 300 mg BID/ritonavir 100 mg BID, 9 days	10 mg QD for 4 days	↑3.4-fold	↑2.25-fold
Telaprevir 750 mg q8h, 10 days	20 mg, SD	↑7.88-fold	↑10.6-fold

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC	Change in Cmax
^{#, †} Ritonavir Saquinavir 400 mg BID/saquinavir ritonavir 400 mg BID, 15 days	40 mg QD for 4 days	↑3.9-fold	↑4.3-fold

[‡]The dose of saquinavir plus ritonavir in this study is not the clinically used dose. The increase in atorvastatin exposure when used clinically is likely to be higher than what was observed in this study. Therefore caution should be applied and the lowest dose necessary should be used.

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC ^{&}	Change in Cmax ^{&}
[#] Lopinavir 400 mg BID/ ritonavir 100 mg BID, 14 days	20 mg QD for 4 days	⊖5.9 fold	⊖4.7 fold

Under 12 CLINICAL PHARMACOLOGY, 12.3 Pharmacokinetics, TABLE 4. Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs:

Atorvastatin	Co-administered drug and dosing regimen		
	Drug/Dose (mg)	Change in AUC	Change in C _{max}
<u>10 mg, SD</u>	<u>Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days</u>	<u>No change</u>	<u>No change</u>
<u>10 mg QD for 4 days</u>	<u>Fosamprenavir 1400 mg BID, 14 days</u>	<u>↓27%</u>	<u>↓18%</u>
<u>10 mg QD for 4 days</u>	<u>Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days</u>	<u>No change</u>	<u>No change</u>

Pravastatin:

Under 12 CLINICAL PHARMACOLOGY, 12.2 Pharmacokinetics, Table 3: Effect of Coadministered Drugs on the Pharmacokinetics of Pravastatin:

Coadministered Drug and Dosing Regimen	Pravastatin		
	Dose (mg)	Change in AUC	Change in C _{max}
<u>Darunavir 600 mg BID/Ritonavir 100 mg BID for 7 days</u>	<u>40 mg single dose</u>	<u>↑81%</u>	<u>↑63%</u>
<u>Kaletra 400 mg/100 mg BID for 14 days</u>	<u>20 mg OD for 4 days</u>	<u>↑33%</u>	<u>↑26%</u>

Under 12 CLINICAL PHARMACOLOGY, 12.2 Pharmacokinetics, Table 4: Effect of Pravastatin on the Pharmacokinetics of Coadministered Drugs

Pravastatin Dosing Regimen	Name and Dose	Change in AUC	Change in C _{max}
<u>20 mg OD for 4 days</u>	<u>Kaletra 400 mg/100 mg BID for 14 days</u>	<u>No change</u>	<u>No change</u>

A December 6, 2011 OCP review of DDI's with lovastatin noted that available data support a contraindication with strong CYP3A4 inhibitors, such as the HIV protease inhibitors. The data were summarized as follows:

- *According to the Guidance for Industry Drug Interaction Studies, lovastatin is listed as one of the sensitive in vivo CYP3A4 substrates. Therefore, strong CYP3A4 inhibitors are predicted to significantly increase lovastatin exposure because lovastatin is extensively metabolized by CYP3A4 isozyme.*
- *Literature survey indicates that itraconazole increases lovastatin exposure up to 15- to 20-fold and the drug interaction seems to result in rhabdomyolysis. Itraconazole is the representative strong CYP3A4 inhibitor and therefore, the effect of itraconazole on lovastatin exposure can be extrapolated to other strong CYP3A4 inhibitors listed in the Guidance as well as the FDA website.*

- *Strong CYP3A4 inhibitors are contraindicated for simvastatin because of the significant drug interaction and its potential for the increased risk on the rhabdomyolysis. Physicochemical and pharmacokinetic properties of lovastatin are comparable with those of simvastatin. Meanwhile, itraconazole increased the exposure of lovastatin (up to 20-fold) more than that of simvastatin (up to 13-fold), and it indicates that strong CYP3A4 inhibitor can cause greater lovastatin exposure increase compared to that of simvastatin. Therefore, it seems reasonable to extrapolate the effect of strong CYP3A4 inhibitors on simvastatin to that on lovastatin.*

Therefore, concomitant use of lovastatin with HIV protease inhibitors, as well as the HCV protease inhibitors boceprevir and telaprevir, will be contraindicated.

Lovastatin:

Under **CONTRAINDICATIONS:**

Concomitant administration with strong CYP3A4 inhibitors, e.g., itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone)

Under **WARNINGS, Myopathy/Rhabdomyolysis, Strong inhibitors of CYP3A4:**

Lovastatin, like several other inhibitors of HMG-CoA reductase, is a substrate of cytochrome P450 3A4 (CYP3A4). When lovastatin is used with a strong inhibitor of CYP3A4, elevated plasma levels of HMG-CoA reductase inhibitory activity can increase the risk of myopathy and rhabdomyolysis, particularly with higher doses of lovastatin. Certain drugs which inhibit this metabolic pathway can raise the plasma levels of lovastatin and may increase the risk of myopathy. These include itraconazole, ketoconazole, and posaconazole, the macrolide antibiotics erythromycin and clarithromycin, and the ketolide antibiotic telithromycin, HIV protease inhibitors, boceprevir, telaprevir, or the antidepressant nefazodone. Combination of these drugs with lovastatin is contraindicated.

Under **WARNINGS, Myopathy/Rhabdomyolysis, Table VII: Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis:**

Interacting Agents	Prescribing Recommendations
Itraconazole Ketoconazole Posaconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Boceprevir Telaprevir Nefazodone	<u>Avoid- Contraindicated</u> with lovastatin

Under **PRECAUTIONS, Drug Interactions, CYP3A4 Interactions:**

Lovastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. Strong inhibitors of CYP3A4 (e.g., below itraconazole, ketoconazole, posaconazole, clarithromycin, telithromycin, HIV protease inhibitors, bocprevir, telaprevir, nefazodone), and large quantities of grapefruit juice increase the risk of myopathy by reducing the elimination of lovastatin.

Itraconazole

Ketoconazole

Erythromycin

Clarithromycin

Telithromycin

HIV protease inhibitors

Nefazodone

Large quantities of grapefruit juice (>1 quart daily)

4. Increases in HbA1c and fasting plasma glucose – TSI #891

On April 8, 2010 TSI #891 was opened to evaluate the effect of statins on increases in HbA1c and fasting plasma glucose. This was based on findings from the JUPITER trial, which reported a 27% increase in investigator-reported diabetes mellitus in rosuvastatin-exposed subjects compared to placebo-exposed subjects. High-dose atorvastatin had previously been associated with worsening glycemic control in the PROVE-IT TIMI 22 substudy.

Several articles from the published literature were also considered, including:

- Sattar N et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomized statin trials. *Lancet*.2010;375:735-742
- Sukhija R et al. Effect of Statins on Fasting Plasma Glucose in Diabetic and Nondiabetic Patients. *Journal of Investigative Medicine*.2009;57(3): 495-499
- Rajpathak SN et al. Statin Therapy and Risk of Developing Type 2 Diabetes: A Meta-Analysis. *Diabetes Care*.2009;32:1924-1929
- Koh KK et al. Atorvastatin Causes Insulin Resistance and Increases Ambient Glycemia in Hypercholesterolemic Patients. *JACC*.2010;55(12):1209-1216
- Thongtang N et al. Effects of Maximal Atorvastatin and Rosuvastatin Treatment on Markers of Glucose Homeostasis and Inflammation. *Am J Cardiol*.2011;107:387-392
- Kostapanos MS et al. Do Statins Beneficially or Adversely Affect Glucose Homeostasis? *Current Vascular Pharmacology*.2010;8:612-631
- Mills EJ et al. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170255 patients from 76 randomized trials. *Q J Med*.2011;104:109-124

- Culver AL et al. Statin Use and Risk of Diabetes Mellitus in Postmenopausal Women in the Women’s Health Initiative. *Arch Intern Med*. Published online January 9, 2012.

The Sattar meta-analysis, which looked at 13 statin trials with 91,140 participants, reported that “statin therapy was associated with a 9% increased risk for incident diabetes (odds ratio [OR] 1.09; 95% CI 1.02-1.17), with little heterogeneity ($I^2=11%$) between trials.”

The Rajpathak meta-analysis, which looked at 6 statin trials with 57,593 participants, reported a “small increase in diabetes risk” (relative risk [RR] 1.13; 95% CI 1.03-1.23), with “no evidence of heterogeneity across trials”.

The Mills meta-analysis, which looked at 76 randomized clinical trials (RCTs) with 170,255 participants, reported that 17 RCTs reported on increased risk of development of incident diabetes (Odds ratio [OR] 1.09; 95% CI 1.02-1.17, $p=0.001$, $I^2=11%$).

Culver et al looked at postmenopausal women participating in the Women’s Health Initiative (WHI) to investigate whether the incidence of new-onset diabetes mellitus is associated with statin use. The study involved 153,840 women. Statin use at baseline was associated with an increased risk of DM (hazard ratio [HR], 1.71; 95% CI, 1.61-1.83); the multivariate-adjusted HR was 1.48; 95% CI, 1.38-1.59. The association was observed for all types of statin medications.

At the time of approval of the JUPITER supplement, the following labeling was required for CRESTOR:

5.5 Endocrine Effects

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including CRESTOR.

The data for an effect of statins on incident diabetes, and increases in HbA1c and/or fasting plasma glucose seem to indicate a class effect; however, given the limitations of epidemiological data, and the findings from the West of Scotland Coronary Prevention Study (WOSCOPS) clinical trial, which suggested that pravastatin may decrease the incidence of diabetes by 30%, the division did not seek a labeling change for pravastatin.

Therefore, based on clinical trial data, epidemiological data, and the published literature, the following labeling change was requested for all statins except pravastatin:

5.X Endocrine Function:

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including <<STATIN>>.

5. Drug-drug interaction with ranolazine – TSI #988

TSI #988 was opened by the Division of Cardiovascular and Renal Products (DCRP) in July 2010 when during routine data monitoring of the AERS database for cases of ranolazine and torsades de pointes, a signal was identified for rhabdomyolysis in patients receiving ranolazine and statins.

Nine cases of drug interaction were related to concomitant use of ranolazine and a statin. Of those nine cases, seven (all male) involved the statin associated adverse events of rhabdomyolysis (6) and myalgia (1). Four of those six patients were stable on long-term statin therapy prior to the initiation of ranolazine. Most cases involved the use of simvastatin.

According to the OCP review:

Ranolazine and SV are both cleared via CYP3A metabolism. Hence, concomitant administration of the two may lead to pharmacokinetic DDI. Administration of ranolazine (1000 mg twice daily) with SV (80 mg once daily) resulted in a ~2-fold increase in C_{max} and ~1.5-fold increase in AUC of SV and SVA, at steady state. Increased systemic exposure to SV and SVA has been associated with increased risk of myopathy and rhabdomyolysis. The 80 mg dose of SV has been shown to be associated with increased incidence of myopathy and rhabdomyolysis. In addition, there is little gain in effectiveness of the 80 mg over 40 mg dose. The DMEP regulatory briefing held on 6/4/2010 suggested progressive removal of 80 mg dose of simvastatin from the market, leaving 40 mg as the highest available dose. Therefore, given the 2-fold increase in systemic exposure expected on concomitant administration of ranolazine and SV, limiting the dose of SV to 20 mg will avoid exposures similar or greater to that observed with 80 mg.

In addition, for other statins which are primarily metabolized by CYP3A (e.g., lovastatin and atorvastatin), concomitant medications which are CYP3A inhibitors are expected to elevate statin exposure, and risk of myopathy. However, at present, definitive data (such as available with simvastatin) is not available for other statins, in order to recommend dose-adjustments.

On June 8, 2011, in conjunction with the approval of new dosing restrictions with the 80 mg dose of simvastatin, DMEP approved a dose cap of simvastatin 20 mg when simvastatin is coadministered with ranolazine.

In addition, the current ranolazine label recommends a dose adjustment of sensitive CYP3A4 substrates such as lovastatin based on the 2-fold simvastatin exposure increase by ranolazine.

Based on the information above, the following recommendations for labeling changes were made:

Mevacor:

Under **WARNINGS, *Myopathy/Rhabdomyolysis***:

Ranolazine: The risk of myopathy, including rhabdomyolysis, may be increased by concomitant administration of ranolazine. Dose adjustment of lovastatin may be considered during co-administration.

Under **PRECAUTIONS, *Other Drug Interactions***:

Ranolazine: The risk of myopathy, including rhabdomyolysis, may be increased by concomitant administration of ranolazine.

Altprev:



Advicor:



6. Myopathy with concomitant administration with colchicine

In June 2010, a Regulatory Briefing was conducted to discuss the increased risk of myopathy, including rhabdomyolysis, associated with the use of simvastatin 80

mg, based on DMEP's review of the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) clinical trial. In preparation for the briefing, OSE noted an interaction between statins and colchicine resulting in an increased risk of myopathy. Colchicine, a substrate of P-glycoprotein and CYP3A4, carried the following information in its label:

5.4 Neuromuscular Toxicity

Colchicine-induced neuromuscular toxicity and rhabdomyolysis have been reported with chronic treatment in therapeutic doses. Patients with renal dysfunction and elderly patients, even those with normal renal and hepatic function, are at increased risk. Concomitant use of atorvastatin, simvastatin, pravastatin, fluvastatin, gemfibrozil, fenofibrate, fenofibric acid, or bezafibrate (themselves associated with myotoxicity) or cyclosporine may potentiate the development of myopathy. Once colchicine is stopped, the symptoms generally resolve within 1 week to several months.

This was based on reports from the literature as summarized in the table below, and adapted from a 2008 OCP review of NDA 22-352 (Colstat [colchicine tablets]).

Lipid Lowering Agents			
HMG-CoA Reductase Inhibitors	Simvastatin: Baker et al. (2004) ; Hsu et al. (2002)	Both are CYP3A4 and P-gp substrates; P-gp inhibition by simvastatin	Acute myopathy or rhabdomyolysis (could be attributed to either drug)
	Fluvastatin: Atasoyu et al. (2005)	Synergistic myotoxicity via PK & PD mechanism; fluvastatin is not a P-gp inhibitor	
	Pravastatin: Alayli et al. (2005)	Synergistic myotoxicity via PK & PD mechanism; pravastatin is not a P-gp inhibitor	
	Atorvastatin: Tufan et al. (2006)	Both are CYP3A4 substrates; P-gp inhibition by atorvastatin	
Fibrates	Gemfibrozil: Atmaca et al., 2002	Synergistic toxic effect of both drugs	
	Fenofibrate & Diltiazem: Sinsawaiwong et al., 1997	Mechanism-based inhibition of CYP3A4 by diltiazem.	

On June 8, 2011, the following changes were approved for the simvastatin-containing drugs:

5 WARNINGS AND PRECAUTIONS

5.1 Myopathy/Rhabdomyolysis

Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be exercised when prescribing simvastatin with colchicine.

7 DRUG INTERACTIONS

7.7 Colchicine

Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be exercised when prescribing simvastatin with colchicine.

In order to harmonize and update the appropriate statin labels, similar labeling changes were requested for atorvastatin, pravastatin, and fluvastatin. Furthermore, because of physicochemical and pharmacokinetic similarities between lovastatin and simvastatin, similar labeling changes were requested for lovastatin.

7. Myopathy with concomitant administration with fibrates

A National Institutes of Health (NIH) funded trial, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid Trial, was reviewed by DMEP and discussed at an Advisory Committee meeting on May 19, 2011. ACCORD-Lipid evaluated the occurrence of major adverse cardiovascular events (MACE), a composite of nonfatal heart attack, nonfatal stroke, and cardiovascular death in patients receiving simvastatin plus fenofibrate, compared to simvastatin alone. The trial found that there was no difference in cardiovascular outcomes between the two groups (Hazard Ratio = 0.92; 95% Confidence Interval: 0.79-1.08; p=0.32).

This was the second failed cardiovascular outcome trial for fenofibrate. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, fenofibrate demonstrated a non-significant 11% relative reduction in the primary outcome of coronary heart disease events (Hazard Ratio = 0.89; 95% Confidence Interval: 0.75-1.05; p=0.04) versus placebo.

The absence to date of proven cardiovascular benefit with fenofibrates must be viewed in the context of observational data showing an increase in the risk of myopathy with fenofibrates, especially when co-administered with a statin. In 2011, OSE conducted a review of observational data on rhabdomyolysis with fenofibrates and gemfibrozil in combination with statins. Their review looked at 3 studies:

- Graham DJ, Staffa JA, Shatin D et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585-2590.
- Amend KL, Landon J, Thyagarajan V, Niemcryk S, McAfee A. Incidence of hospitalized rhabdomyolysis with statin and fibrate use in an insured US population. *Ann Pharmacother* 2011;45:1230-1239.
- Enger C, Gately R, Ming EE, Niemcryk SJ, Williams L, McAfee AT. Pharmacoepidemiology safety study of fibrate and statin concomitant therapy. *Am J Cardiol* 2010;106:1594-1601.

According to the OSE review, the best available evidence suggests that fenofibrate-statin combination is associated with an increased hazard rate for rhabdomyolysis (HR, 3.26, 95% CI, 1.21-8.80) relative to statin monotherapy. There also appears to be a differential risk associated with the gemfibrozil-statin combination therapy versus the fenofibrate-statin combination therapy, with a

numerically higher rate of rhabdomyolysis observed with gemfibrozil-statin combination therapy (HR, 11.93, 95% CI, 3.96-35.93) compared to statin monotherapy.

Most statin labels contain language in the FPI (Warnings and Precautions and Drug Interactions sections) regarding the increased risk of myopathy, including rhabdomyolysis, when statins and fibrates are co-administered. In order to highlight this increased risk, as well as to note the differential risk between gemfibrozil-statin combination therapy and fenofibrate-statin combination therapy, all sponsors of statin drugs with labels in the PLR format (i.e., all except the lovastatin products) were requested to add the following information to the Highlights page. The following language was also provided in the Drug Interactions section of the PI's, depending on the level of risk determined for each statin product:

-----**DRUG INTERACTIONS**-----

Other Lipid-lowering Medications: Use with other fibrate products or lipid-modifying doses (≥ 1 g/day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with <<STATIN>>.

7.X Lipid-Lowering Drugs That Can Cause Myopathy When Given Alone

Gemfibrozil: <<Contraindicated or Avoid>> with <<STATIN>>

Other fibrates: Caution should be used when prescribing with <<STATIN>>

7.X Gemfibrozil

Due to an increased risk of myopathy/rhabdomyolysis when HMG-CoA reductase inhibitors are coadministered with gemfibrozil, concomitant administration of <<STATIN>> with gemfibrozil should be avoided.

7.X Other Fibrates

Because it is known that the risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of other fibrates, <<STATIN>> should be administered with caution when used concomitantly with other fibrates.

8. Myopathy with concomitant administration with lipid-modifying doses of niacin

In March 2010, DMEP approved a labeling revision for simvastatin based on interim results from an ongoing clinical trial - the Heart Protection Study 2 (HPS2) – Treatment of HDL to Reduce the Incidence of Vascular Events (THRIVE), a cardiovascular outcome trial being conducted in 20,000 patients with vascular disease from the UK, China and Scandinavia to investigate whether combining niacin with a new drug (laropiprant) that minimizes niacin's flushing effect can reduce the risk of serious heart attacks and strokes among people already taking treatment to lower their LDL-cholesterol. The interim HPS2 – THRIVE results showed that the incidence of myopathy was higher in patients of

Chinese descent (0.43%) compared with patients not of Chinese descent (0.03%) taking 40 mg simvastatin plus cholesterol-modifying doses (≥ 1 g/day) of a niacin-containing product. The exact mechanism of this drug interaction is not fully understood.

Drug-drug interaction studies report an increase in simvastatin exposure of 41-64% with co-administration of simvastatin and ER niacin. According to OCP, the cause of the observed changes in exposure of simvastatin due to ER niacin is not well established as this is not due to changes in the known pathways (e.g., via CYP3A4 or OATP1B1). Furthermore, a PK study of simvastatin in Chinese subjects showed no significant differences in Chinese and non-Asian subjects in simvastatin C_{max} and AUC_{0-last} , and simvastatin acid AUC_{0-last} or C_{max} .

The OCP Genomics Group further noted that the SLCO1B1 genotype that has been associated with statin-induced myopathy, is less prevalent in Asian populations than European populations and, therefore, does not seem to explain the higher myopathy risk rates among Chinese subjects in HPS2-THRIVE.

So, it remains unclear if this increased risk of myopathy with statin and niacin co-administration is unique to Chinese subjects, or applies to other Asians and non-Asians as well.

Furthermore, in the AIM-HIGH study, which compared ER-niacin with simvastatin to simvastatin alone in reducing the residual cardiovascular risk in patients with established cardiovascular disease, “there was no incremental clinical benefit from the addition of niacin to statin therapy during a 36-month follow-up period, despite significant improvements in HDL cholesterol and triglyceride levels”.

The lack of clear benefit in conjunction with uncertainty as to the nature of the increased risk of myopathy in patients treated with niacin plus a statin led FDA to believe that this risk needed to be highlighted in statin labeling.

The labeling approved for simvastatin in March 2010 noted that patients of Chinese descent should not receive simvastatin 80 mg with cholesterol-modifying doses of niacin-containing products.

In June 2011, in conjunction with labeling revisions required based on the Agency’s review of the SEARCH trial, this language was modified to note that “caution should be used when treating Chinese patients with simvastatin doses exceeding 20 mg/day coadministered with lipid-modifying doses of niacin-containing products.”

Most statin labels contain information in the FPI (Warnings and Precautions and Drug Interactions sections) noting that “The risk of skeletal muscle effects may be enhanced when <<STATIN>> is used in combination with niacin; a reduction in

<<STATIN>> dosage should be considered in this setting.” All sponsors of statin drugs with labels in the PLR format were requested to modify the HIGHLIGHTS page, with corresponding changes to the FPI if indicated, as follows:

-----DRUG INTERACTIONS-----

Other Lipid-lowering Medications: Use with other fibrate products or lipid-modifying doses (≥ 1 g/day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with <<STATIN>>.

7.X Niacin

The risk of skeletal muscle effects may be enhanced when <<STATIN>> is used in combination with lipid-modifying doses (≥ 1 g/day) of niacin; a reduction in <<STATIN>> dosage should be considered in this setting.

9. Update to lovastatin drug-drug interactions and dose caps

Subsequent to the June 2011 labeling revisions to the simvastatin-containing products which were largely based on the SEARCH clinical trial data and the increased risk of myopathy associated with the 80 mg dose of simvastatin, a review of drug-drug interactions with lovastatin was conducted. The physicochemical and pharmacokinetic properties of lovastatin are comparable with those of simvastatin. Lovastatin is a sensitive *in vivo* CYP3A4 substrate; therefore, strong CYP3A4 inhibitors are predicted to significantly increase lovastatin exposure. According to OCP:

Itraconazole increased the exposure of lovastatin (up to 20-fold) more than that of simvastatin (up to 13-fold), and it indicates that strong CYP3A4 inhibitor can cause greater lovastatin exposure increase compared to that of simvastatin. Therefore, it seems reasonable to extrapolate the effect of strong CYP3A4 inhibitors on simvastatin to that on lovastatin.

Based on available studies from the literature, as well as extrapolation from simvastatin data, the following changes to the lovastatin label were recommended:

Under **CONTRAINDICATIONS:**

Concomitant administration with strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone).

Under **WARNINGS, Myopathy/Rhabdomyolysis, Strong Potent inhibitors of CYP3A4:**

Lovastatin, like several other inhibitors of HMG-CoA reductase, is a substrate of cytochrome P450 3A4 (CYP3A4). ~~When lovastatin is used with a potent inhibitor of~~

CYP3A4, elevated plasma levels of HMG-CoA reductase inhibitory activity can increase the risk of myopathy and rhabdomyolysis, particularly with higher doses of lovastatin. Certain drugs which inhibit this metabolic pathway can raise the plasma levels of lovastatin and may increase the risk of myopathy. These include itraconazole, ketoconazole, and posaconazole, the macrolide antibiotics erythromycin and clarithromycin, and the ketolide antibiotic telithromycin, HIV protease inhibitors, boceprevir, telaprevir, or the antidepressant nefazodone. Combination of these drugs with lovastatin is contraindicated.

~~The use of lovastatin concomitantly with the potent CYP3A4 inhibitors itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily) should be avoided.~~ Concomitant use of other medicines labeled as having a potent strong inhibitory effect on CYP3A4 should be avoided unless the benefits of combined therapy outweigh the increased risk. If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with lovastatin should be suspended during the course of treatment.

Although not studied clinically, voriconazole has been shown to inhibit lovastatin metabolism *in vitro* (human liver microsomes). Therefore, voriconazole is likely to increase the plasma concentration of lovastatin. It is recommended that dose adjustment of lovastatin be considered during coadministration. Increased lovastatin concentration in plasma has been associated with an increased risk of myopathy/rhabdomyolysis.

Under **WARNINGS, Myopathy/Rhabdomyolysis:**

~~Gemfibrozil, particularly with higher doses of lovastatin: The dose of lovastatin should not exceed 20 mg daily in patients receiving concomitant medication with gemfibrozil. The combined use of lovastatin with gemfibrozil should be avoided, unless the benefits are likely to outweigh the increased risks of this drug combination.~~

~~Other lipid-lowering drugs (other fibrates or ≥ 1 g/day of niacin): The dose of lovastatin should not exceed 20 mg daily in patients receiving concomitant medication with other fibrates or ≥ 1 g/day of niacin.~~ Caution should be used when prescribing other fibrates or lipid-lowering doses (≥ 1 g/day) of niacin with lovastatin, as these agents can cause myopathy when given alone. **The benefit of further alterations in lipid levels by the combined use of lovastatin with other fibrates or niacin should be carefully weighed against the potential risks of these combinations.**

Cyclosporine: The use of lovastatin with cyclosporine should be avoided.

~~Cyclosporine or dDanazol, diltiazem or verapamil with higher doses of lovastatin: The dose of lovastatin should not exceed 20 mg daily in patients receiving concomitant medication with cyclosporine or danazol, diltiazem, or verapamil.~~ The benefits of the use of lovastatin in patients receiving cyclosporine or danazol, diltiazem, or verapamil should be carefully weighed against the risks of these combinations.

~~Amiodarone or verapamil: The dose of lovastatin should not exceed 40 mg daily in patients receiving concomitant medication with amiodarone or verapamil.~~ The combined use of lovastatin at doses higher than 40 mg daily with amiodarone or verapamil should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy. The risk of myopathy/rhabdomyolysis is

increased when either amiodarone or verapamil is used concomitantly with higher doses of a closely related member of the HMG-CoA reductase inhibitor class.

Under **WARNINGS, Myopathy/Rhabdomyolysis:**

Cyclosporine: The use of lovastatin with cyclosporine should be avoided.

~~Amiodarone or verapamil:~~ The dose of lovastatin should not exceed 40 mg daily in patients receiving concomitant medication with amiodarone or verapamil. The combined use of lovastatin at doses higher than 40 mg daily with amiodarone or verapamil should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy. The risk of myopathy/rhabdomyolysis is increased when either amiodarone or verapamil is used concomitantly with higher doses of a closely related member of the HMG-CoA reductase inhibitor class.

~~Cyclosporine, or Danazol, diltiazem or verapamil~~ with higher doses of lovastatin: The dose of lovastatin should not exceed 20 mg daily in patients receiving concomitant medication with cyclosporine, or danazol, diltiazem, or verapamil. The benefits of the use of lovastatin in patient receiving cyclosporine, or danazol, diltiazem, or verapamil should be carefully weighed against the risks of these combinations.

Under **WARNINGS, Myopathy/Rhabdomyolysis, Table VII: Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis:**

Interacting Agents	Prescribing Recommendations
Ketoconazole Itraconazole Posaconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Boceprevir Telaprevir Nefazodone	Avoid <u>Contraindicated</u> with lovastatin
<u>Gemfibrozil</u> Cyclosporine	<u>Avoid with lovastatin</u>
Gemfibrozil Other fibrates Lipid lowering doses (≥1 g/day) of niacin Cyclosporine Danazol <u>Diltiazem</u> <u>Verapamil</u>	Do not exceed 20 mg lovastatin daily
Amiodarone Verapamil	Do not exceed 40 mg lovastatin daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)

Under **PRECAUTIONS, Drug Interactions, CYP3A4 Interactions:**

Lovastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. ~~Potent~~ Strong inhibitors of CYP3A4 (e.g., below itraconazole, ketoconazole, posaconazole, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone and erythromycin), and large quantities of grapefruit juice increase the risk of myopathy by reducing the elimination of lovastatin

Itraconazole
Ketoconazole
Erythromycin
Clarithromycin
Telithromycin
HIV protease inhibitors
Nefazodone
Large quantities of grapefruit juice (>1 quart daily)

In vitro studies have demonstrated that voriconazole inhibits the metabolism of lovastatin. Adjustment of the lovastatin dose may be needed to reduce the risk of myopathy, including rhabdomyolysis, if voriconazole must be used concomitantly with lovastatin.

Under **PRECAUTIONS**, *Other Drug Interactions*:

~~Cyclosporine or Danazol~~: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporine ~~or danazol~~ particularly with higher doses of lovastatin.

Danzol, Diltiazem, or Verapamil: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of danazol, diltiazem, or verapamil particularly with higher doses of lovastatin.

~~Amiodarone or Verapamil~~: The risk of myopathy/rhabdomyolysis is increased when either amiodarone ~~or verapamil~~ is used concomitantly with a closely related member of the HMG-CoA reductase inhibitor class.

Under **PRECAUTIONS**, *Endocrine Function*:

Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ~~ketoconazole~~, spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

Under **DOSAGE AND ADMINISTRATION**:

Dosage in Patients taking ~~Cyclosporine or Danazol, Diltiazem, or Verapamil~~
In patients taking ~~cyclosporine or danazol, diltiazem, or verapamil~~ concomitantly with lovastatin, therapy should begin with 10 mg of lovastatin and should not exceed 20 mg/day.

Dosage in Patients taking Amiodarone ~~or Verapamil~~
In patients taking amiodarone ~~or verapamil~~ concomitantly with MEVACOR, the dose should not exceed 40 mg/day.

Concomitant Lipid-Lowering Therapy

MEVACOR is effective alone or when used concomitantly with bile-acid sequestrants. ~~If MEVACOR is used in combination with gemfibrozil, other fibrates or lipid lowering doses (\geq 1g/day) of niacin, the dose of MEVACOR should not exceed 20 mg/day.~~

Under **CLINICAL PHARMACOLOGY**:

	Number of Subjects	Dosing of Coadministered Drug or Grapefruit Juice	Dosing of Lovastatin	AUC Ratio* (with / without coadministered drug) No Effect = 1.00	
				Lovastatin	Lovastatin acid [†]
Gemfibrozil	11	600 mg BID for 3 days	40 mg	0.96	2.80
Itraconazole [‡]	12	200 mg QD for 4 days	40 mg on Day 4	> 36 [§]	22
	10	100 mg QD for 4 days	40 mg on Day 4	> 14.8 [§]	15.4
Grapefruit Juice [¶] (high dose)	10	200 mL of double-strength TID [#]	80 mg single dose	15.3	5.0
Grapefruit Juice [¶] (low dose)	16	8 oz (about 250 mL) of single-strength [‡] for 4 days	40 mg single dose	1.94	1.57
Cyclosporine	16	Not described ^β	10 mg QD for 10 days	5- to 8-fold	ND ^α
	Number of Subjects	Dosing of Coadministered Drug or Grapefruit Juice	Dosing of Lovastatin	AUC Ratio* (with / without coadministered drug) No Effect = 1.00 Total Lovastatin acid [‡]	
Diltiazem	10	120 mg BID for 14 days	20 mg	3.57 [‡]	

* Results based on a chemical assay

[†] Lovastatin acid refers to the β-hydroxyacid of lovastatin

[‡] The mean total AUC of lovastatin without itraconazole phase could not be determined accurately. Results could be representative of strong CYP3A4 inhibitors such as ketoconazole, posaconazole, clarithromycin, telithromycin, HIV protease inhibitors, and nefazodone

[§] Estimated minimum change

[¶] The effect of amounts of grapefruit juice between those used in these two studies on lovastatin pharmacokinetics has not been studied

[#] Double-strength: one can of frozen concentrate diluted with one can of water. Grapefruit juice was administered TID for 2 days, and 200 mL together with single dose lovastatin and 30 and 90 minutes following single dose lovastatin on Day 3

[‡] Single-strength: one can of frozen concentrate diluted with 3 cans of water. Grapefruit juice was administered with breakfast for 3 days, and lovastatin was administered in the evening on Day 3

^β Cyclosporine-treated patients with psoriasis or post kidney or heart transplant patients with stable graft function, transplanted at least 9 months prior to study

10. Update to simvastatin and lovastatin drug-drug interaction:

In May 2011, the hepatitis C protease inhibitors boceprevir and telaprevir were approved. These protease inhibitors have been characterized as being strong CYP3A4 inhibitors. Because simvastatin is contraindicated with strong CYP3A4 inhibitors, and because the simvastatin label individually lists strong CYP3A4 inhibitors with which simvastatin is contraindicated, these two recently approved protease inhibitors will be added to the list in all simvastatin-containing products (Zocor, Vytorin, and Simcor).

Because of the physicochemical and pharmacokinetic similarities between simvastatin and lovastatin, and consistent with changes being made to the lovastatin labeling which include a new contraindication with strong CYP3A4 inhibitors, the labeling for lovastatin will be modified to add boceprevir and telaprevir to the list of strong CYP3A4 inhibitors with which lovastatin is contraindicated.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY G EGAN
02/27/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
021366Orig1s024

OTHER REVIEW(S)

Division of Metabolism & Endocrine Products

Labeling Review

Application Number: NDA 21-366/S-024

Name of Drug: Crestor (rosuvastatin) Tablets

Sponsor: AstraZeneca

Submission Date: September 28, 2011 and Final PI/PPI: February 14, 2012 email

Background and Summary:

Crestor is indicated:

1. as an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Type IIa and IIb);
2. as an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson Type IV);
3. to reduce LDL-C, total-C, and ApoB in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.
4. slowing of the progression of atherosclerosis

It is supplied in the tablet dose strengths of 5, 10, 20, and 40 mg.

Supplement S-021 was the last approved Package Insert (PI) that provided for the addition of “depression” and “sleep disorders (including insomnia and nightmares)” to the **ADVERSE REACTIONS, Postmarketing Experience** subsection of the CRESTOR package insert.

Supplement S-024 is a “Prior Approval” supplemental new drug application provides for revisions to the **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS** sections of the Highlights of Prescribing Information section and changes to the **DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS,** and **PATIENT COUNSELING INFORMATION** sections of the Full Prescribing Information sections of the CRESTOR (rosuvastatin) package insert, and corresponding revisions to the CRESTOR (rosuvastatin) patient package insert

Review:

A track change version including all labeling changes since the last approved label and a final, clean version of the PI and PPI have been attached to the approval letter.

At the request of AstraZeneca (see attached email dated January 10, 2012), in Section 11 **DESCRIPTION**, the PI was revised to include the following language: “**CRESTOR** Tablets for oral administration contain 5, 10, 20, or 40 mg of rosuvastatin and the following...” Additionally, to the PPI, the following language was added:

What are the Ingredients in CRESTOR?

Active Ingredient: **rosuvastatin as** rosuvastatin calcium

Conclusion:

The PI and PPI submitted on February 14, 2012, by email, were deemed acceptable by Dr. Amy Egan. Dr. Su Tran was consulted on January 10, 2012, regarding the **DESCRIPTION** section of the PI and the “**What are the Ingredients in CRESTOR?**” section of the PPI. A formal review was not required because the labeling request was viewed as a correction to an editorial error. Agency will issue an approval letter on this labeling supplement.

Reviewed by: M.A. Simoneau, R.Ph., Regulatory Project Manager/2.20.212

Simoneau, Margaret A

From: Tran, Suong T
Sent: Tuesday, January 10, 2012 1:42 PM
To: Simoneau, Margaret A
Subject: FW: NDA 21-366 - CRESTOR label question
Attachments: Prohotsky JPS 2012.pdf; annotated_draft_label1 submitted with S-010.pdf; S-010 Approval Letter.pdf; 021366s021lbl - Current CRESTOR PI - FDA website.pdf

Hi Peggy!

Yes, the applicant's proposal is acceptable, no CMC review will be needed because this is only to correct an editorial error.

Thanks for the update,
 Su

From: Simoneau, Margaret A
Sent: Tuesday, January 10, 2012 1:26 PM
To: Tran, Suong T
Cc: Egan, Amy
Subject: FW: NDA 21-366 - CRESTOR label question

Su- As discussed, if you find this labeling change acceptable, we will include the information in the PI that we are planning to AP by the end of January. Please let me know if you need any additional information regarding supplement S-010 as referenced in the sponsor's email.

Thanks again.

From: DeFeo, Pat A [mailto:pat.defeo@astrazeneca.com]
Sent: Tuesday, January 10, 2012 12:09 PM
To: Simoneau, Margaret A
Cc: Egan, Amy
Subject: NDA 21-366 - CRESTOR label question

Dear Margaret,

As follow-up to my voice mail message of this morning, attached please find an article that has recently been brought to our attention which discusses the inconsistent practice of expression of drug strengths for drugs containing salt forms. Rosuvastatin calcium (CRESTOR) is mentioned on page 2 in the next to last paragraph.

Prior to the approval for the atherosclerosis indication (NDA 21-366/S-010) when the Physician's Labeling Rule was first applied to revise the format of the CRESTOR label, the following statement appeared in the "DESCRIPTION" section of the PI:



Upon approval of the atherosclerosis indication (November 8, 2007), a similar statement was included in Section 11 "DESCRIPTION" but the initial part of the paragraph was deleted [REDACTED] (b) (4) and the statement was changed to the following:

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

In summary, the current US label implies that [REDACTED] (b) (4)

[REDACTED] AstraZeneca believes the label should be revised to include the original statement as above, as this better describes the actual composition of CRESTOR tablets and clarifies the drug strength expression of rosuvastatin.

In addition to the body of the PI, we propose also adding the following language (in red) to the PPI section of the CRESTOR label:

"What are the Ingredients in CRESTOR?
Active Ingredient: **rosuvastatin as** rosuvastatin calcium
Inactive Ingredients: microcrystalline cellulose NF, lactose monohydrate NF, tribasic calcium phosphate NF, crospovidone NF, magnesium stearate NF, hypromellose NF, triacetin NF, titanium dioxide USP, yellow ferric oxide, and red ferric oxide NF."

I have attached the following versions of the CRESTOR label for your convenience:

- The annotated version included with the atherosclerosis submission for NDA 21-366 (S-010), submitted on January 8, 2007
- The November 8, 2007 approval letter for NDA 21-366/S-010 with the approved label included
- The currently approved CRESTOR USPI with PPI

AstraZeneca will soon be submitting a revised label for CRESTOR containing safety updates that are the result of internal reviews. Would it be appropriate to include the above revised wording as part of that safety update or do you recommend another route for re-introducing this wording?

Thank you for your consideration. Please let me know if you have any questions regarding this. I look forward to hearing from you.

Best regards,
Pat

Patricia A. DeFeo, MS
US Regulatory Affairs Director, CV

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/s/

MARGARET A SIMONEAU
02/20/2012