CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021366Orig1s046

Trade Name:	CRESTOR
Generic or Proper Name:	rosuvastatin
Sponsor:	AstraZeneca UK LTD
Approval Date:	July 31, 2024
Indication:	CRESTOR is an HMG Co-A reductase inhibitor (statin) indicated: •To reduce the risk of major adverse cardiovascular (CV) events (CV death, nonfatal myocardial infarction, nonfatal stroke, or an arterial revascularization procedure) in adults without established coronary heart disease who are at increased risk of CV disease based on age, high-sensitivity C-reactive protein (hsCRP) ≥2 mg/L, and at least one additional CV risk factor. •As an adjunct to diet to: o reduce LDL-C in adults with primary hyperlipidemia. o reduce LDL-C and slow the progression of atherosclerosis in adults. o reduce LDL-C in adults and pediatric patients aged 8 years and older with heterozygous familial hypercholesterolemia (HeFH).

•As an adjunct to other LDL-C-lowering therapies, or alone if such treatments are unavailable, to reduce LDL-C in adults and pediatric patients aged 7 years and older with homozygous familial hypercholesterolemia (HoFH).

•As an adjunct to diet for the treatment of adults with:
- Primary dysbetalipoproteinemia.
- Hypertriglyceridemia

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

NDA 021366/S-046

SUPPLEMENT APPROVAL

AstraZeneca UK Limited
C/O: AstraZeneca Pharmaceuticals LP
Attention: Sally Walsh
Senior Regulatory Affairs Director
One MedImmune Way
Gaithersburg, MD 20878

Dear Sally Walsh:

Please refer to your supplemental new drug application (sNDA) dated and received May 10, 2024, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Crestor (rosuvastatin calcium) tablets.

This Prior Approval sNDA provides for the following updates to the Crestor Prescribing Information and the Patient Package Insert:

- Revised the indication statement in Section 1 *Indications and Usage* to better describe the overall effect of the composite endpoint and to provide consistency in labeling major adverse cardiovascular events (MACE) endpoints:
    - From: To reduce the risk of stroke, myocardial infarction, and arterial revascularization procedures in adults without established coronary heart disease who are at increased risk of cardiovascular (CV) disease based on age, hsCRP ≥2 mg/L, and at least one additional CV risk factor.
    - To: To reduce the risk of major adverse cardiovascular (CV) events (CV death, nonfatal myocardial infarction, nonfatal stroke, or an arterial. revascularization procedure) in adults without established coronary heart disease who are at increased risk of CV disease based on age, high-sensitivity C-reactive protein (hsCRP) ≥2 mg/L, and at least one additional CV risk factor.
- Minor revisions were made to Sections 2.1 *General Dosage and Administration Information* and 2.6 *Dosage Modifications Due to Drug Interactions*.
- Modified Table 5 in Section 7.1 *Drug Interactions that Increase the Risk of Myopathy and Rhabdomyolysis with CRESTOR* to include drug interaction information with ticagrelor.
- Updated America's Poison Centers in Section 10 *Overdosage* to current name that removes the term "control."

- Revised the Patient Package Insert for consistency with the full Prescribing Information. Additional revisions were made to reduce redundancy, to make patient information more consistent and concise, and to include the information necessary for patients to safely take their medication.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling with minor editorial revisions listed below and reflected in the enclosed labeling.

- Revision dates in the Highlights of Prescribing Information and Patient Package Insert were updated to reflect supplement approval.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

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 FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient 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 *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes 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 Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

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, contact Martin White, MS, Regulatory Project Manager, at 240-402-6018.

Sincerely,

{See appended electronic signature page}

John Sharretts, M.D.
Director
Division of Diabetes, Lipid Disorders, and Obesity
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOHN M SHARRETTS
07/31/2024 04:31:40 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021366Orig1s046

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) tablets, for oral use
Initial U.S. Approval: 2003

---------- RECENT MAJOR CHANGES ----------
Indications and Usage (1) 07/2024

---------- INDICATIONS AND USAGE ----------
CRESTOR is an HMG Co-A reductase inhibitor (statin) indicated: (1)

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

---------- DOSAGE AND ADMINISTRATION ----------
Take orally with or without food, at any time of day. (2.1)
Assess LDL-C when clinically appropriate, as early as 4 weeks after initiating CRESTOR, and adjust dosage if necessary. (2.1)
Adults: Recommended dosage range is 5 to 40 mg once daily. (2.1)
Pediatric Patients with HeFH: Recommended dosage range is 5 to 10 mg once daily for patients aged 8 to less than 10 years of age, and 5 to 20 mg once daily for patients aged 10 years and older. (2.2)
Pediatric Patients with HoFH: Recommended dosage is 20 mg once daily for patients aged 7 years and older. (2.2)
Asian Patients: Initiate at 5 mg once daily. Consider risks and benefits of treatment if not adequately controlled at doses up to 20 mg once daily. (2.4)
Patients with Severe Renal Impairment (not on hemodialysis): Initiate at 5 mg once daily; do not exceed 10 mg once daily. (2.5)
See full prescribing information for CRESTOR dosage and administration modifications due to drug interactions. (2.6)

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

---------- CONTRAINDICATIONS ----------
Acute liver failure or decompensated cirrhosis. (4)
Hypersensitivity to rosuvastatin or any excipients in CRESTOR. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- *Myopathy and Rhabdomyolysis:* Risk factors include age 65 years or greater, uncontrolled hypothyroidism, renal impairment, concomitant use with certain other drugs, and higher CRESTOR dosage. Asian patients may be at higher risk for myopathy. Discontinue CRESTOR if markedly elevated CK levels occur or myopathy is diagnosed or suspected. Temporarily discontinue CRESTOR in patients experiencing an acute or serious condition at high risk of developing renal failure secondary to rhabdomyolysis. Inform patients of the risk of myopathy and rhabdomyolysis when starting or increasing CRESTOR dosage. Instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. (5.1)
- *Immune-Mediated Necrotizing Myopathy (IMNM):* Rare reports of IMNM, an autoimmune myopathy, have been reported with statin use. Discontinue CRESTOR if IMNM is suspected. (5.2)
- *Hepatic Dysfunction:* Increases in serum transaminases have occurred, some persistent. Rare reports of fatal and non-fatal hepatic failure have occurred. Consider testing liver enzymes before initiating therapy and as clinically indicated thereafter. If serious hepatic injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs, promptly discontinue CRESTOR. (5.3)

---------- ADVERSE REACTIONS ----------
Most frequent adverse reactions (rate ≥2%) are headache, nausea, myalgia, asthenia, and constipation. (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 ----------
See full prescribing information for details regarding concomitant use of CRESTOR with other drugs that increase the risk of myopathy and rhabdomyolysis. (7.1)
Aluminum and Magnesium Hydroxide Combination Antacids: Administer CRESTOR at least 2 hours before the antacid. (7.2)
Warfarin: Obtain INR prior to starting CRESTOR. Monitor INR frequently until stable upon initiation, dose titration or discontinuation. (7.3)

---------- USE IN SPECIFIC POPULATIONS ----------

- *Pregnancy:* May cause fetal harm. (8.1)
- *Lactation:* Breastfeeding not recommended during treatment with CRESTOR. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 07/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CRESTOR is indicated:

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

2 DOSAGE AND ADMINISTRATION

2.1 General Dosage and Administration Information

- Administer CRESTOR orally as a single dose at any time of day, with or without food. Swallow the tablets whole.
- Assess LDL-C when clinically appropriate, as early as 4 weeks after initiating CRESTOR, and adjust the dosage if necessary.
- If a dose is missed, advise patients not to take an extra dose. Resume treatment with the next dose.
- When taking CRESTOR with an aluminum and magnesium hydroxide combination antacid, administer CRESTOR at least 2 hours before the antacid *[see Drug Interactions (7.2)]*.

2.2 Recommended Dosage in Adult Patients

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

2.3 Recommended Dosage in Pediatric Patients

Dosage in Pediatric Patients 8 Years of Age and Older with HeFH

The recommended dosage range is 5 mg to 10 mg orally once daily in patients aged 8 years to less than 10 years and 5 mg to 20 mg orally once daily in patients aged 10 years and older.

Dosage in Pediatric Patients 7 Years of Age and Older with HoFH

The recommended dosage is 20 mg orally once daily.

2.4 Dosing in Asian Patients

Initiate CRESTOR at 5 mg once daily due to increased rosuvastatin plasma concentrations. Consider the risks and benefits of CRESTOR when treating Asian patients not adequately controlled at doses up to 20 mg once daily *[see Warnings and Precautions (5.1), Use in Specific Populations (8.8), and Clinical Pharmacology (12.3)]*.

2.5 Recommended Dosage in Patients with Renal Impairment

In patients with severe renal impairment (CL_{cr} less than 30 mL/min/1.73 m^2) not on hemodialysis, the recommended starting dosage is 5 mg once daily and should not exceed 10 mg once daily *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)]*.

There are no dosage adjustment recommendations for patients with mild and moderate renal impairment.

2.6 Dosage Modifications Due to Drug Interactions

Table 1 displays dosage modifications for CRESTOR due to drug interactions *[see Warnings and Precautions (5.1) and Drug Interactions (7.1)]*.

Table 1: CRESTOR Dosage Modifications Due to Drug Interactions

Concomitantly Used Drug	CRESTOR Dosage Modifications
Cyclosporine	Do not exceed 5 mg once daily.
Teriflunomide	Do not exceed 10 mg once daily.
Enasidenib	Do not exceed 10 mg once daily.
Capmatinib	Do not exceed 10 mg once daily.
Fostamatinib	Do not exceed 20 mg once daily.

Febuxostat	Do not exceed 20 mg once daily.
Gemfibrozil	Avoid concomitant use. If used concomitantly, initiate at 5 mg once daily and do not exceed 10 mg once daily.
Tafamidis	Avoid concomitant use. If used concomitantly, initiate at 5 mg once daily and do not exceed 20 mg once daily.
Antiviral Medications	
○ Sofbuvir/velpatasvir/voxilaprevir ○ Ledipasvir/sofosbuvir	Concomitant use not recommended.
○ Simeprevir ○ Dasabuvir/ombitasvir/paritaprevir/ritonavir ○ Elbasvir/Grazoprevir ○ Sofosbuvir/Velpatasvir ○ Glecaprevir/Pibrentasvir ○ Atazanavir/Ritonavir ○ Lopinavir/Ritonavir	Initiate at 5 mg once daily. Do not exceed 10 mg once daily.
Darolutamide	Do not exceed 5 mg once daily.
Regorafenib	Do not exceed 10 mg once daily.

3 DOSAGE FORMS AND STRENGTHS

CRESTOR tablets:

- 5 mg of rosuvastatin: yellow, round, biconvex, coated tablets. Debossed “ZD4522” and “5” on one side of the tablet.
- 10 mg of rosuvastatin: pink, round, biconvex, coated tablets. Debossed “ZD4522” and “10” on one side of the tablet.
- 20 mg of rosuvastatin: pink, round, biconvex, coated tablets. Debossed “ZD4522” and “20” on one side of the tablet.
- 40 mg of rosuvastatin: pink, oval, biconvex, coated tablets. Debossed “ZD4522” on one side and “40” on the other side of the tablet.

4 CONTRAINDICATIONS

CRESTOR is contraindicated in the following conditions:

- Acute liver failure or decompensated cirrhosis *[see Warnings and Precautions (5.3)]*.
- Hypersensitivity to rosuvastatin or any excipients in CRESTOR. Hypersensitivity reactions including rash, pruritus, urticaria, and angioedema have been reported with CRESTOR *[see Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Myopathy and Rhabdomyolysis

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

Risk Factors for Myopathy

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

Steps to Prevent or Reduce the Risk of Myopathy and Rhabdomyolysis

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

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

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

5.2 Immune-Mediated Necrotizing Myopathy

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

5.3 Hepatic Dysfunction

Increases in serum transaminases have been reported with use of CRESTOR *[see Adverse Reactions (6.1)]*. In most cases, these changes appeared soon after initiation, were transient, were not accompanied by symptoms, and resolved or improved on continued therapy or after a brief interruption in therapy. In a pooled analysis of placebo-controlled trials, increases in serum transaminases to more than three times the ULN occurred in 1.1% of patients taking CRESTOR versus 0.5% of patients treated with placebo. Marked persistent increases of hepatic transaminases have also occurred with CRESTOR. There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including CRESTOR.

Patients who consume substantial quantities of alcohol and/or have a history of liver disease may be at increased risk for hepatic injury *[see Use in Specific Populations (8.7)]*.

Consider liver enzyme testing before CRESTOR initiation and when clinically indicated thereafter. CRESTOR is contraindicated in patients with acute liver failure or decompensated cirrhosis *[see Contraindications (4)]*. If serious hepatic injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs, promptly discontinue CRESTOR.

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 statins, though it was generally transient and was not associated with worsening renal function. Although the clinical significance of this finding is unknown, consider a dose reduction for patients on CRESTOR therapy with unexplained persistent proteinuria and/or hematuria during routine urinalysis testing.

5.5 Increases in HbA1c and Fasting Serum Glucose Levels

Increases in HbA1c and fasting serum glucose levels have been reported with statins, including CRESTOR. Based on clinical trial data with CRESTOR, in some instances these increases may exceed the threshold for the diagnosis of diabetes mellitus *[see Adverse Reactions (6.1)]*. Optimize lifestyle measures, including regular exercise, maintaining a healthy body weight, and making healthy food choices.

6 ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

Myopathy and Rhabdomyolysis *[see Warnings and Precautions (5.1)]*
Immune-Mediated Necrotizing Myopathy *[see Warnings and Precautions (5.2)]*
Hepatic Dysfunction *[see Warnings and Precautions (5.3)]*
Proteinuria and Hematuria *[see Warnings and Precautions (5.4)]*

Increases in HbA1c and Fasting Serum Glucose Levels *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

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

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

Table 2: Adverse Reactions Reported in ≥2% of Patients Treated with CRESTOR and > Placebo in Placebo-Controlled Trials

Adverse Reactions	Placebo N=382 %	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 %
Headache	5.0	5.5	4.9	3.1	8.5	5.5
Nausea	3.1	3.8	3.5	6.3	0	3.4
Myalgia	1.3	3.1	2.1	6.3	1.9	2.8
Asthenia	2.6	2.4	3.2	4.7	0.9	2.7
Constipation	2.4	2.1	2.1	4.7	2.8	2.4

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

In the METEOR study, patients were treated with CRESTOR 40 mg (n=700) or placebo (n=281) with a mean treatment duration of 1.7 years. Adverse reactions reported in ≥2% of patients and at a rate greater than placebo are shown in Table 3.

Table 3: Adverse Reactions Reported in ≥2% of Patients Treated with CRESTOR and > Placebo in the METEOR Trial

Adverse Reactions	Placebo N=281 %	CRESTOR 40 mg N=700 %
Myalgia	12.1	12.7
Arthralgia	7.1	10.1
Headache	5.3	6.4
Dizziness	2.8	4.0
Increased CPK	0.7	2.6
Abdominal pain	1.8	2.4
ALT greater than 3x ULN[1]	0.7	2.2

[1] Frequency recorded as abnormal laboratory value.

In the JUPITER study, patients were treated with CRESTOR 20 mg (n=8,901) or placebo (n=8,901) for a mean duration of 2 years. In JUPITER, there was a significantly higher frequency of diabetes mellitus reported in patients taking CRESTOR (2.8%) versus patients taking placebo (2.3%). Mean HbA1c was significantly increased by 0.1% in CRESTOR-treated patients compared to placebo-treated patients. The number of patients with a HbA1c >6.5% at the end of the trial was significantly higher in CRESTOR-treated versus placebo-treated patients *[see Clinical Studies (14)]*.

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

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

Adverse Reactions	**Placebo N=8,901 %**	**CRESTOR 20 mg N=8,901 %**
Myalgia	6.6	7.6
Arthralgia	3.2	3.8
Constipation	3.0	3.3
Diabetes mellitus	2.3	2.8
Nausea	2.3	2.4

Pediatric Patients with HeFH

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

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of CRESTOR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood Disorders: thrombocytopenia

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

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

Nervous System Disorders: peripheral neuropathy, rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, and confusion) associated with the use of all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks). There have been rare reports of new-onset or exacerbation of myasthenia gravis, including ocular myasthenia, and reports of recurrence when the same or a different statin was administered.

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

Reproductive System and Breast Disorders: gynecomastia

Respiratory Disorders: interstitial lung disease

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

7 DRUG INTERACTIONS

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

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

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

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

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

	• Atazanavir/ritonavir • Lopinavir/ritonavir	CRESTOR 10 mg once daily.
Darolutamide		
Clinical Impact:	Darolutamide increased rosuvastatin exposure more than 5-fold. The risk of myopathy and rhabdomyolysis is increased with concomitant use.	
Intervention:	In patients taking darolutamide, do not exceed a dose of CRESTOR 5 mg once daily.	
Regorafenib		
Clinical Impact:	Regorafenib increased rosuvastatin exposure and may increase the risk of myopathy.	
Intervention:	In patients taking regorafenib, do not exceed a dose of CRESTOR 10 mg once daily.	
Fenofibrates (e.g., fenofibrate and fenofibric acid)		
Clinical Impact:	Fibrates may cause myopathy when given alone. The risk of myopathy and rhabdomyolysis is increased with concomitant use of fibrates with CRESTOR.	
Intervention:	Consider if the benefit of using fibrates concomitantly with CRESTOR outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy, particularly during initiation of therapy and during upward dose titration of either drug.	
Niacin		
Clinical Impact:	Cases of myopathy and rhabdomyolysis have occurred with concomitant use of lipid-modifying doses (≥1 g/day) of niacin with CRESTOR.	
Intervention:	Consider if the benefit of using lipid-modifying doses (≥1 g/day) of niacin concomitantly with CRESTOR outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy, particularly during initiation of therapy and during upward dose titration of either drug.	
Colchicine		
Clinical Impact:	Cases of myopathy and rhabdomyolysis have been reported with concomitant use of colchicine with CRESTOR.	
Intervention:	Consider if the benefit of using colchicine concomitantly with CRESTOR outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy, particularly during initiation of therapy and during upward dose titration of either drug.	
Ticagrelor		
Clinical Impact:	Concomitant use of CRESTOR and ticagrelor has been shown to increase rosuvastatin concentrations, which may result in increased risk of myopathy. Cases of myopathy and rhabdomyolysis have been reported in patients using both products concomitantly. Cases have occurred more frequently in patients taking 40 mg of rosuvastatin.	
Intervention:	In patients taking concomitant ticagrelor, especially those with additional risk factors for myopathy and rhabdomyolysis, monitor	

	patients for signs and symptoms of myopathy, particularly during initiation of therapy and during upward dose titration of CRESTOR.

7.2 Drug Interactions that Decrease the Efficacy of CRESTOR

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

Table 6: Drug Interactions that Decrease the Efficacy of CRESTOR

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

7.3 CRESTOR Effects on Other Drugs

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

Table 7: CRESTOR Effects on Other Drugs

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

Available data from case series and prospective and retrospective observational cohort studies over decades of use with statins in pregnant women have not identified a drug-associated risk of major congenital malformations. Published data from prospective and retrospective observational cohort studies with CRESTOR use in pregnant women are insufficient to determine if there is a drug-associated risk of miscarriage *(see Data)*.

In animal reproduction studies, no adverse developmental effects were observed in pregnant rats or rabbits orally administered rosuvastatin during the period of organogenesis at doses that resulted in systemic exposures equivalent to human exposures at the maximum recommended human dose (MRHD) of 40 mg/day, based on AUC and body surface area (mg/m^2), respectively *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Human Data

A Medicaid cohort linkage study of 1,152 statin-exposed pregnant women compared to 886,996 controls did not find a significant teratogenic effect from maternal use of statins in the first trimester of pregnancy, after adjusting for potential confounders – including maternal age, diabetes mellitus, hypertension, obesity, and alcohol and tobacco use – using propensity score-based methods. The relative risk of congenital malformations between the group with statin use and the group with no statin use in the first trimester was 1.07 (95% confidence interval 0.85 to 1.37) after controlling for confounders, particularly pre-existing diabetes mellitus. There were also no statistically significant increases in any of the organ-specific malformations assessed after accounting for confounders. In the majority of pregnancies, statin treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. Study limitations include reliance on physician coding to define the presence of a malformation, lack of control for certain confounders such as body mass index, use of prescription dispensing as verification for the use of a statin, and lack of information on non-live births.

Animal Data

In female rats given 5, 15 and 50 mg/kg/day before mating and continuing through to gestation day 7 resulted in decreased fetal body weight (female pups) and delayed ossification at 50 mg/kg/day (10 times the human exposure at the MRHD dose of 40 mg/day based on AUC).

In pregnant rats given 2, 10 and 50 mg/kg/day of rosuvastatin from gestation day 7 through lactation day 21 (weaning), decreased pup survival occurred at 50 mg/kg/day (dose equivalent to 12 times the MRHD of 40 mg/day based body surface area).

In pregnant rabbits given 0.3, 1, and 3 mg/kg/day of rosuvastatin from gestation day 6 to day 18, decreased fetal viability and maternal mortality was observed at 3 mg/kg/day (dose equivalent to the MRHD of 40 mg/day based on body surface area).

Rosuvastatin crosses the placenta in rats and rabbits 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. In rabbits, fetal tissue distribution was 25% of maternal plasma concentration after a single oral gavage dose of 1 mg/kg on gestation day 18.

8.2 Lactation

Risk Summary

Limited data from case reports in published literature indicate that CRESTOR is present in human milk. There is no available information on the effects of the drug on the breastfed infant or the effects of the drug on milk production. Statins, including CRESTOR, decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol and may cause harm to the breastfed infant.

Because of the potential for serious adverse reactions in a breastfed infant, based on the mechanism of action, advise patients that breastfeeding is not recommended during treatment with CRESTOR *[see Use in Specific Populations (8.1) and Clinical Pharmacology (12.1)]*.

8.4 Pediatric Use

The safety and effectiveness of CRESTOR as an adjunct to diet to reduce LDL-C have been established in pediatric patients 8 years of age and older with HeFH. Use of CRESTOR for this indication is based on one 12-week controlled trial with a 40-week open-label extension period in 176 pediatric patients 10 years of age and older with HeFH and one 2-year open-label, uncontrolled trial in 175 pediatric patients 8 years of age and older with HeFH *[*see *Clinical Studies (14)]*. In the 1-year trial with a 12-week controlled phase, there was no detectable effect of CRESTOR on growth, weight, BMI (body mass index), or sexual maturation in patients aged 10 to 17 years.

The safety and effectiveness of CRESTOR as an adjunct to other LDL-C-lowering therapies to reduce LDL-C have been established in pediatric patients 7 years of age and older with HoFH. Use of CRESTOR for this indication is based on a randomized, placebo-controlled, cross-over study in 14 pediatric patients 7 years of age and older with HoFH *[*see *Clinical Studies (14)]*.

The safety and effectiveness of CRESTOR have not been established in pediatric patients younger than 8 years of age with HeFH, younger than 7 years of age with HoFH, or in pediatric patients with other types of hyperlipidemia (other than HeFH or HoFH).

8.5 Geriatric Use

Of the 10,275 patients in clinical studies with CRESTOR, 3,159 (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.

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

8.6 Renal Impairment

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

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

8.7 Hepatic Impairment

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

8.8 Asian Patients

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

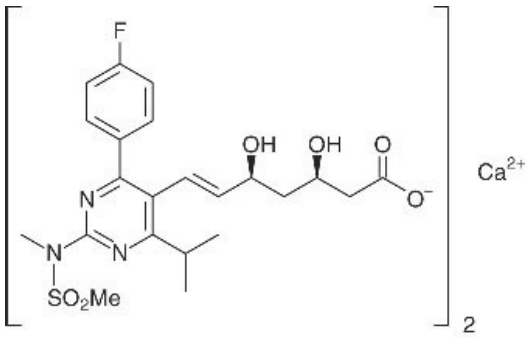
10 OVERDOSAGE

No specific antidotes for CRESTOR are known. Hemodialysis does not significantly enhance clearance of rosuvastatin. In the event of overdose, consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations.

11 DESCRIPTION

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

The chemical name for rosuvastatin calcium is bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt with the following structural formula:



The empirical formula for rosuvastatin calcium is $(C_{22}H_{27}FN_3O_6S)_2Ca$ and the molecular weight is 1,001.14. Rosuvastatin calcium is a white amorphous powder that is sparingly soluble in water and methanol, and slightly soluble in ethanol. Rosuvastatin calcium is a hydrophilic compound with a partition coefficient (octanol/water) of 0.13 at pH of 7.0.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

Absorption

In clinical pharmacology studies in man, peak plasma concentrations of rosuvastatin were reached 3 to 5 hours following oral dosing. Both C_{max} and AUC increased in approximate proportion to CRESTOR dose. The absolute bioavailability of rosuvastatin is approximately 20%. The AUC of rosuvastatin does not differ following evening or morning drug administration.

Effect of food

Administration of CRESTOR with food did not affect the AUC of rosuvastatin.

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.

Elimination

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%). After an intravenous dose, approximately 28% of total body clearance was via the renal route, and 72% by the hepatic route. The elimination half-life of rosuvastatin is approximately 19 hours.

Specific Populations

Geriatric Patients

There were no differences in plasma concentrations of rosuvastatin between the nonelderly and elderly populations (age ≥65 years).

Pediatric Patients

In a population pharmacokinetic analysis of two pediatric trials involving patients with HeFH 10 to 17 years of age and 8 to 17 years of age, respectively, rosuvastatin exposure appeared comparable to or lower than rosuvastatin exposure in adult patients.

Male and Female Patients

There were no differences in plasma concentrations of rosuvastatin between males and females.

Racial or Ethnic Groups

A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among White, Hispanic or Latino ethnicity, 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 White control group.

Patients with Renal Impairment

Mild to moderate renal impairment (CL_{cr} ≥30 mL/min/1.73 m^2) had no influence on plasma concentrations of rosuvastatin. However, plasma concentrations of rosuvastatin increased to a clinically significant extent (about 3-fold) in patients with severe renal impairment (CL_{cr} <30 mL/min/1.73 m^2) not receiving hemodialysis compared with healthy subjects (CL_{cr} >80 mL/min/1.73 m^2).

Steady-state plasma concentrations of rosuvastatin in patients on chronic hemodialysis were approximately 50% greater compared with healthy volunteer subjects with normal renal function.

Patients with 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 Interaction Studies

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

Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter organic anion-transporting polyprotein 1B1 (OATP1B1) and efflux transporter breast cancer resistance protein (BCRP). Concomitant administration of CRESTOR with medications that are inhibitors of these transporter proteins (e.g., cyclosporine, certain HIV protease inhibitors *[see Dosage and Administration (2.6) and Drug Interactions (7.1)]* and ticagrelor *[see Drug Interactions (7.1)]*) may result in increased rosuvastatin plasma concentrations.

Table 8: Effect of Coadministered Drugs on Rosuvastatin Systemic Exposure

Coadministered drug and dosing regimen	**Rosuvastatin**		
		Mean Ratio (ratio with/without coadministered drug) No Effect=1.0	
	Dose (mg)[1]	**Change in AUC**	**Change in C_{max}**
Sofosbuvir/velpatasvir/voxilaprevir (400 mg/100 mg/100 mg) + Voxilaprevir (100 mg) once daily for 15 days	10 mg, single dose	7.39[2] (6.68 to 8.18)[3]	18.88[2] (16.23 to 21.96)[3]
Cyclosporine – stable dose required (75 mg – 200 mg BID)	10 mg, QD for 10 days	7.1[2]	11[2]
Darolutamide 600 mg BID, 5 days	5 mg, single dose	5.2[2]	~5[2]
Regorafenib 160 mg QD, 14 days	5 mg, single dose	3.8[2]	4.6[2]
Atazanavir/ritonavir combination 300 mg/100 mg QD for 8 days	10 mg	3.1[2]	7[2]
Simeprevir 150 mg QD, 7 days	10 mg, single dose	2.8[2] (2.3 to 3.4)[3]	3.2[2] (2.6 to 3.9)[3]
Velpatasvir 100 mg once daily	10 mg, single dose	2.69[2] (2.46 to 2.94)[3]	2.61[2] (2.32 to 2.92)[3]
Ombitasvir 25 mg/paritaprevir 150 mg/ ritonavir 100 mg + dasabuvir 400 mg BID	5 mg, single dose	2.59[2] (2.09 to 3.21)[3]	7.13[2] (5.11 to 9.96)[3]
Teriflunomide	Not available	2.51[2]	2.65[2]
Enasidenib 100 mg QD, 28 days	10 mg, single dose	2.44	3.66
Elbasvir 50 mg/grazoprevir 200 mg once daily	10 mg, single dose	2.26[2] (1.89 to 2.69)[3]	5.49[2] (4.29 to 7.04)[3]
Glecaprevir 400 mg/pibrentasvir 120 mg once daily	5 mg, once daily	2.15[2] (1.88 to 2.46)[3]	5.62[2] (4.80 to 6.59)[3]
Lopinavir/ritonavir combination 400 mg/100 mg BID for 17 days	20 mg, QD for 7 days	2.1[2] (1.7 to 2.6)[3]	5[2] (3.4 to 6.4)[3]
Capmatinib 400 mg BID	10 mg, single dose	2.08[2] (1.56 to 2.76)[3]	3.04[2] (2.36 to 3.92)[3]
Fostamatinib 100 mg BID	20 mg, single dose	1.96[2] (1.77 to 2.15)[3]	1.88[2] (1.69 to 2.09)[3]
Febuxostat 120 mg QD for 4 days	10 mg, single dose	1.9[2] (1.5 to 2.5)[3]	2.1[2] (1.8 to 2.6)[3]
Gemfibrozil 600 mg BID for 7 days	80 mg	1.9[2] (1.6 to 2.2)[3]	2.2[2] (1.8 to 2.7)[3]

Table 8: Effect of Coadministered Drugs on Rosuvastatin Systemic Exposure

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

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

[1] Single dose unless otherwise noted.

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

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

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

Rosuvastatin Dosage Regimen	**Coadministered Drug**		
		Mean Ratio (ratio with/without coadministered drug) No Effect=1.0	
	Name and Dose	**Change in AUC**	**Change in C_{max}**
40 mg QD for 10 days	Warfarin[1] 25 mg single dose	R- Warfarin 1.0 (1.0 to 1.1)[2] S-Warfarin 1.1 (1.0 to 1.1)[2]	R-Warfarin 1.0 (0.9 to 1.0)[2] S-Warfarin 1.0 (0.9 to 1.1)[2]
40 mg QD for 12 days	Digoxin 0.5 mg single dose	1.0 (0.9 to 1.2)[2]	1.0 (0.9 to 1.2)[2]
40 mg QD for 28 days	Oral Contraceptive (ethinyl estradiol 0.035 mg & norgestrel 0.180, 0.215 and 0.250 mg) QD for 21 Days	EE 1.3 (1.2 to 1.3)[2] NG 1.3 (1.3 to 1.4)[2]	EE 1.3 (1.2 to 1.3)[2] NG 1.2 (1.1 to 1.3)[2]

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

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

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

12.5 Pharmacogenomics

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

In a 107-week carcinogenicity study in mice given 10, 60, or 200 mg/kg/day by oral gavage, an increased incidence of hepatocellular adenoma/carcinoma was observed at 200 mg/kg/day at

systemic exposures 20 times the human exposure at 40 mg/day based on AUC. An increased incidence of hepatocellular tumors was not seen at lower doses.

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

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

14 CLINICAL STUDIES

Primary Prevention of CV Disease

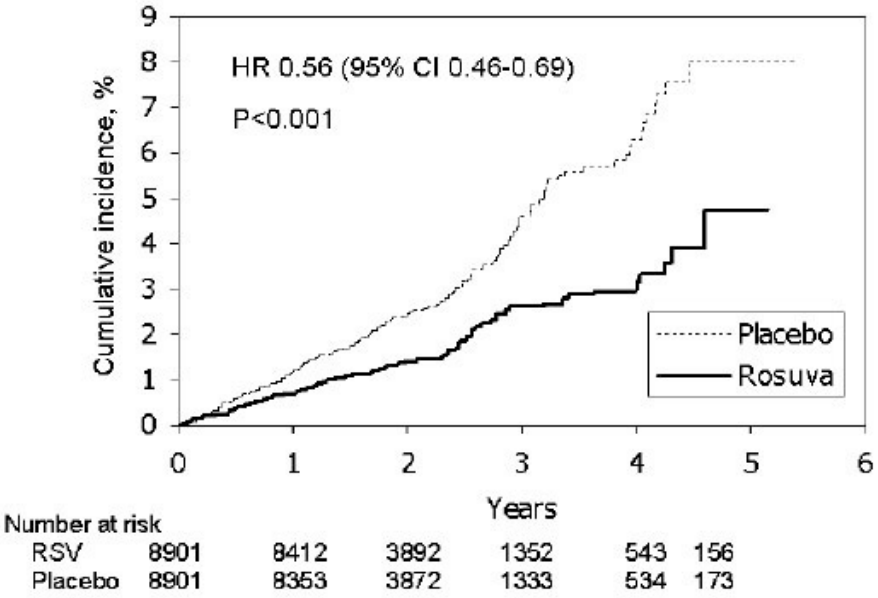
In the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study, the effect of CRESTOR on the occurrence of major CV disease events was assessed in 17,802 males (≥50 years) and females (≥60 years) who had no clinically evident CV disease,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

The primary end point was a composite end point consisting of the time-to-first occurrence of any of the following major CV events: CV death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina or an arterial revascularization procedure.

CRESTOR significantly reduced the risk of major CV events (252 events in the placebo group vs. 142 events in the rosuvastatin group) with a statistically significant ($p<0.001$) relative risk reduction of 44% and absolute risk reduction of 1.2% (see Figure 1). The risk reduction for the primary end point was consistent across the following predefined subgroups: age, sex, race,

smoking status, family history of premature CHD, body mass index, LDL-C, HDL-C, and hsCRP levels.

Figure 1. Time to First Occurrence of Major CV Events in JUPITER

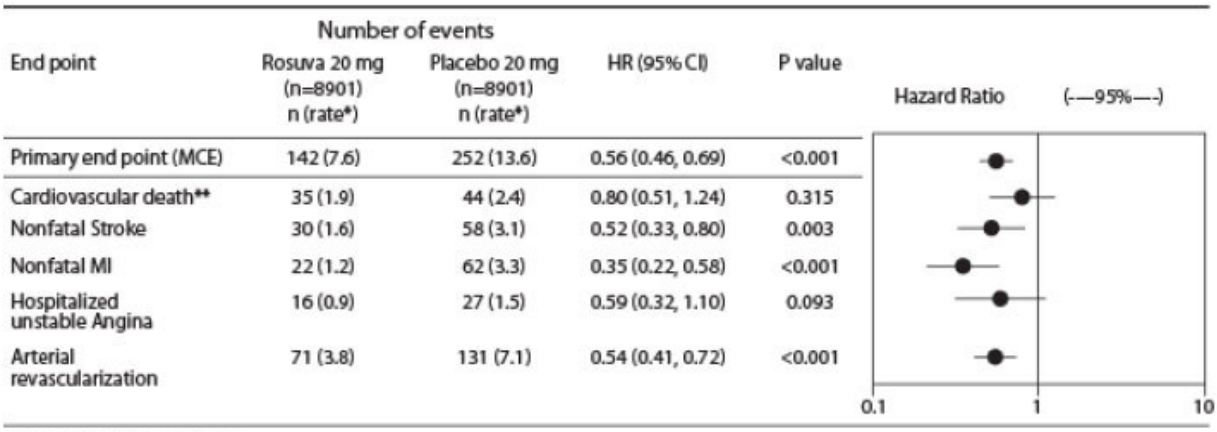


The individual components of the primary end point are presented in Figure 3. CRESTOR significantly reduced the risk of nonfatal myocardial infarction, nonfatal stroke, and arterial revascularization procedures. There were no significant treatment differences between the CRESTOR and placebo groups for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

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

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

Figure 2. Major CV Events by Treatment Group in JUPITER



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

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

Primary Hyperlipidemia in Adults

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

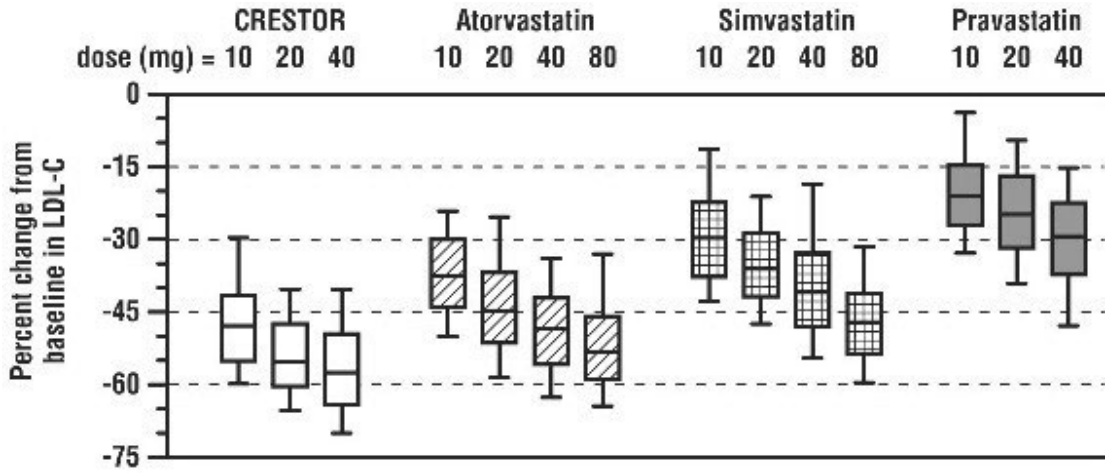
In a multicenter, double-blind, placebo-controlled study in patients with hyperlipidemia, CRESTOR given as a single daily dose (5 to 40 mg) for 6 weeks significantly reduced Total-C, LDL-C, non-HDL-C, and ApoB, across the dose range (Table 10).

Table 10: Lipid-Modifying Effect of CRESTOR in Adult Patients with Hyperlipidemia (Adjusted Mean % Change from Baseline at Week 6)

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

CRESTOR was compared with the statins (atorvastatin, simvastatin, and pravastatin) in a multicenter, open-label, dose-ranging study of 2,240 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 (see Figure 3 and Table 11).

Figure 3. Percent LDL-C Change by Dose of CRESTOR, Atorvastatin, Simvastatin, and Pravastatin at Week 6 in Adult Patients with Hyperlipidemia or Mixed Dyslipidemia



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

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

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

[1] Corresponding standard errors are approximately 1.00.
[2] CRESTOR 10 mg reduced LDL-C significantly more than atorvastatin 10 mg; pravastatin 10 mg, 20 mg, and 40 mg; simvastatin 10 mg, 20 mg, and 40 mg. ($p<0.002$)
[3] CRESTOR 20 mg reduced LDL-C significantly more than atorvastatin 20 mg and 40 mg; pravastatin 20 mg and 40 mg; simvastatin 20 mg, 40 mg, and 80 mg. ($p<0.002$)
[4] CRESTOR 40 mg reduced LDL-C significantly more than atorvastatin 40 mg; pravastatin 40 mg; simvastatin 40 mg, and 80 mg. ($p<0.002$)

Slowing of the Progression of Atherosclerosis

In the *Measuring Effects on Intima Media Thickness: an Evaluation Of Rosuvastatin 40 mg (METEOR)* study, the effect of therapy with CRESTOR on carotid atherosclerosis was assessed by B-mode ultrasonography in patients with elevated LDL-C, at low risk (Framingham risk <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 adult 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.

HeFH in Adults

In a study of adult patients with HeFH (baseline mean LDL of 291 mg/dL), patients were randomized to CRESTOR 20 mg or atorvastatin 20 mg. The dose was increased at 6-week intervals. Significant LDL-C reductions from baseline were seen at each dose in both treatment groups (see Table 12).

Table 12: LDL-C Percent Change from Baseline

		CRESTOR (n=435) LS Mean[1] (95% CI)	**Atorvastatin (n=187) LS Mean[1] (95% CI)**
Week 6	20 mg	-47% (-49%, -46%)	-38% (-40%, -36%)
Week 12	40 mg	-55% (-57%, -54%)	-47% (-49%, -45%)
Week 18	80 mg	NA	-52% (-54%, -50%)

[1] LS Means are least square means adjusted for baseline LDL-C

HeFH in Pediatric Patients

In a double-blind, randomized, multicenter, placebo-controlled, 12-week study, 176 (97 male and 79 female) pediatric patients with HeFH were randomized to rosuvastatin 5 mg, 10 mg 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 13 below.

Table 13: Lipid-Modifying Effects of CRESTOR in Pediatric Patients 10 to 17 years of Age with HeFH (Least-Squares Mean Percent Change from Baseline To Week 12)

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

[1] Median percent change
[2] Difference from placebo not statistically significant

Rosuvastatin was also studied in a two-year open-label, uncontrolled, titration-to-goal trial that included 175 pediatric patients with HeFH who were 8 to 17 years old (79 males and 96 females). All patients had a documented genetic defect in the LDL receptor or in ApoB. Approximately 89% were White, 7% were Asian, 1% were Black or African American, and fewer than 1% were Hispanic or Latino ethnicity. Mean LDL-C at baseline was 236 mg/dL. Fifty-eight (33%) patients were prepubertal at baseline. The starting rosuvastatin dosage for all pediatric patients was 5 mg once daily. Pediatric patients aged 8 to less than 10 years (n=41 at baseline) could titrate to a maximum dosage of 10 mg once daily, and pediatric patients aged 10 to 17 years could titrate to a maximum dosage of 20 mg once daily.

The reductions in LDL-C from baseline were generally consistent across age groups within the trial as well as with previous experience in both adult and pediatric controlled trials.

HoFH in Adult and Pediatric Patients

In an open-label, forced-titration study, HoFH 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-C 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.

HoFH in Pediatric Patients

CRESTOR was studied in a randomized, double-blind, placebo-controlled, multicenter, cross-over study in 14 pediatric patients with HoFH. The study included a 4-week dietary lead-in phase during which patients received CRESTOR 10 mg daily, a cross-over phase that included two

6-week treatment periods with either CRESTOR 20 mg or placebo in random order, followed by a 12-week open-label phase during which all patients received CRESTOR 20 mg. Patients ranged in age from 7 to 15 years of age (median 11 years), 50% were male, 71% were White, 21% were Asian, 7% were Black or African American, and no patients were of Hispanic or Latino ethnicity. Fifty percent were on apheresis therapy and 57% were taking ezetimibe. Patients who entered the study on apheresis therapy or ezetimibe continued the treatment throughout the entire study. Mean LDL-C at baseline was 416 mg/dL (range 152 to 716 mg/dL). A total of 13 patients completed both treatment periods of the randomized cross-over phase; one patient withdrew consent due to inability to have blood drawn during the cross-over phase.

CRESTOR 20 mg significantly reduced LDL-C, total cholesterol, ApoB, and non-HDL-C compared to placebo (see Table 14).

Table 14: Lipid-Modifying Effects of CRESTOR in Pediatric Patients 7 to 15 years of Age with HoFH After 6 Weeks

	Placebo (N=13)	**CRESTOR 20 mg (N=13)**	**Percent difference (95% CI)**
LDL-C (mg/dL)	481	396	-22.3% (-33.5, -9.1)[1]
Total-C (mg/dL)	539	448	-20.1% (-29.7, -9.1)[2]
Non-HDL-C (mg/dL)	505	412	-22.9% (-33.7, -10.3)[2]
ApoB (mg/dL)	268	235	-17.1% (-29.2, -2.9)[3]

% Difference estimates are based on transformations of the estimated mean difference in log LDL measurements between CRESTOR and placebo using a mixed model adjusted for study period
[1] p=0.005, [2] p=0.003, [3] p=0.024

Primary Dysbetalipoproteinemia in Adults

In a randomized, multicenter, double-blind cross-over study, 32 adult patients (27 with ϵ2/ϵ2 and 4 with apo E mutation [Arg145Cys] with primary dysbetalipoproteinemia 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 for 6 weeks each: rosuvastatin 10 mg followed by rosuvastatin 20 mg or rosuvastatin 20 mg followed by rosuvastatin 10 mg. CRESTOR reduced non-HDL-C (primary end point) and circulating remnant lipoprotein levels. Results are shown in the table below.

Table 15: Lipid-Modifying Effects of CRESTOR 10 mg and 20 mg in Adult Patients with 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)
Non-HDL-C	294.5	-48.2 (-56.7, -45.6)	-56.4 (-61.4, -48.5)
VLDL-C + IDL-C	209.5	-46.8 (-53.7, -39.4)	-56.2 (-67.7, -43.7)
LDL-C	112.5	-54.4 (-59.1, -47.3)	-57.3 (-59.4, -52.1)
HDL-C	35.5	10.2 (1.9, 12.3)	11.2 (8.3, 20.5)
RLP-C	82.0	-56.4 (-67.1, -49.0)	-64.9 (-74.0, -56.6)
Apo-E	16.0	-42.9 (-46.3, -33.3)	-42.5 (-47.1, -35.6)

Hypertriglyceridemia in Adults

In a double-blind, placebo-controlled study in adult 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 (see Table 16).

Table 16: Lipid-Modifying Effect of CRESTOR in Adult Patients with Primary Hypertriglyceridemia After Six Weeks by Median (Min, Max) Percent Change from Baseline to Week 6

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)
Non-HDL-C	2 (-13, 19)	-29 (-43, -8)	-49 (-59, -20)	-43 (-74, 12)	-51 (-62, -6)
Total-C	1 (-13, 17)	-24 (-40, -4)	-40 (-51, -14)	-34 (-61, -11)	-40 (-51, -4)
LDL-C	5 (-30, 52)	-28 (-71, 2)	-45 (-59, 7)	-31 (-66, 34)	-43 (-61, -3)
HDL-C	-3 (-25, 18)	3 (-38, 33)	8 (-8, 24)	22 (-5, 50)	17 (-14, 63)

16 HOW SUPPLIED/STORAGE AND HANDLING

CRESTOR tablets are supplied as:

Strength	How Supplied	NDC	Tablet Description
5 mg	bottles of 90 tablets	0310-7560-90	Yellow, round, biconvex, coated tablets. Debossed “ZD4522” and “5” on one side
10 mg	bottles of 90 tablets	0310-7570-90	Pink, round, biconvex, coated tablets. Debossed “ZD4522” and “10” on one side
20 mg	bottles of 90 tablets	0310-7580-90	Pink, round, biconvex, coated tablets. Debossed “ZD4522” and “20” on one side

40 mg	bottles of 30 tablets	0310-7590-30	Pink, oval, biconvex, coated tablets. Debossed "ZD4522" on one side and "40" on the other side

Storage

Store at controlled room temperature, 20ºC to 25ºC (68ºF to 77ºF); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Myopathy and Rhabdomyolysis

Advise patients that CRESTOR may cause myopathy and rhabdomyolysis. Inform patients that the risk is also increased when taking certain types of medication and they should discuss all medication, both prescription and over-the-counter, with their healthcare provider. Instruct patients to promptly report any unexplained muscle pain, tenderness or weakness particularly if accompanied by malaise or fever *[see Warnings and Precautions (5.1), and Drug Interactions (7.1)]*.

Hepatic Dysfunction

Inform patients that CRESTOR may cause liver enzyme elevations and possibly liver failure. Advise patients to promptly report fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice *[see Warnings and Precautions (5.3)]*.

Increases in HbA1c and Fasting Serum Glucose Levels

Inform patients that increases in HbA1c and fasting serum glucose levels may occur with CRESTOR. Encourage patients to optimize lifestyle measures, including regular exercise, maintaining a healthy body weight, and making healthy food choices *[see Warnings and Precautions (5.5)]*.

Pregnancy

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

Lactation

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

Concomitant Use of Antacids

When taking CRESTOR with an aluminum and magnesium hydroxide combination antacid, administer CRESTOR at least 2 hours before the antacid *[see Drug Interactions (7.2)]*.

Missed Doses

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

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Wilmington, DE 19850

PATIENT INFORMATION
CRESTOR® (Kres-tor)
(rosuvastatin)
tablets, for oral use

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

What is CRESTOR?

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

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

It is not known if CRESTOR is safe and effective in children younger than 8 years of age with HeFH or children younger than 7 years of age with HoFH or in children with other types of hyperlipidemias (other than HeFH or HoFH).

Do not take CRESTOR if you:

- have liver problems.
- are allergic to rosuvastatin or any of the ingredients in CRESTOR. See the end of this leaflet for a complete list of ingredients in CRESTOR.

Before you take CRESTOR, tell your healthcare provider about all of your medical conditions, including if you:

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

- are breastfeeding. CRESTOR can pass into your breast milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby if you take CRESTOR. Do not breastfeed while taking CRESTOR.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Tell your healthcare provider who prescribes CRESTOR if another healthcare provider increases the dose of another medicine you are taking.
CRESTOR may affect the way other medicines work, and other medicines may affect how CRESTOR works.

Especially tell your healthcare provider if you take:

- coumarin anticoagulants (medicines that prevent blood clots, such as warfarin)
- antacids (medicines you take for heartburn that contain aluminum and magnesium hydroxide

Taking CRESTOR with certain medicines may increase the risk of muscle problems.

Especially tell your healthcare provider if you take:

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

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

How should I take CRESTOR?

- Take CRESTOR exactly as your healthcare provider tells you to take it.
- Take CRESTOR, by mouth, 1 time each day, with or without food. Swallow the tablet whole.
- CRESTOR can be taken at any time of day, with or without food.
- **Do not** change your dose or stop CRESTOR without talking to your healthcare provider, even if you are feeling well.

- Your healthcare provider may do blood tests to check your cholesterol levels before and during your treatment with CRESTOR. Your healthcare provider may change your dose of CRESTOR if needed.
- While taking CRESTOR, continue to follow your cholesterol-lowering diet and to exercise as your healthcare provider told you to.
- If you take a medicine called an antacid that contains a combination of aluminum and magnesium hydroxide, take CRESTOR at least 2 hours before you take the antacid.
- If you miss a dose of CRESTOR, take your next dose at your normal scheduled time. **Do not take** an extra dose of CRESTOR**.**
- In case of an overdose, get medical help or contact a live Poison Center expert right away at 1-800-222-1222. Advice is also available online at poisonhelp.org.

What are the possible side effects of CRESTOR?

CRESTOR may cause serious side effects, including:

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

Your chances of getting muscle problems are higher if you:

- are taking certain other medicines while you take CRESTOR (see "Especially tell your healthcare provider if you take")
- are 65 years of age or older
- are of Asian descent
- have thyroid problems (hypothyroidism) that are not controlled
- have kidney problems
- are taking higher doses of CRESTOR

- **Liver problems.** Your healthcare provider may do blood tests to check your liver before you start taking CRESTOR and if you have symptoms of liver problems while you take CRESTOR. Call your healthcare provider right away if you have any of the following symptoms of liver problems:
  - feel unusually tired or weak
  - loss of appetite
  - upper belly pain
  - dark urine
  - yellowing of your skin or the whites of your eyes
- **Protein and blood in the urine.** CRESTOR may cause you to have protein and blood in your urine. If you develop protein or blood in your urine, your healthcare provider may decrease your dose of CRESTOR.
- **Increase in blood sugar (glucose) levels**. CRESTOR may cause an increase in your blood sugar levels.

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

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

For more information, ask your healthcare provider or pharmacist.

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

How should I store CRESTOR?

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

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

General Information about the safe and effective use of CRESTOR

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use CRESTOR for a condition for which it was not prescribed. Do not give CRESTOR to other people, even if they have the same medical condition you have. It may harm them.

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

What are the Ingredients in CRESTOR?

Active Ingredient: rosuvastatin as rosuvastatin calcium

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

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Wilmington, DE 19850
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This Patient Information has been approved by the U.S. Food and Drug Administration Revised 07/2024

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021366Orig1s046

CLINICAL REVIEW(S)

Prior Approval Labeling Supplement-Clinical Memo

NDA:	21366/SD3635/S-46
Sponsor:	IPR Pharmaceuticals (AstraZeneca)
Drug name:	Crestor/rosuvastatin tablets
Date of submission:	May 10, 2024
Type of submission:	Prior Approval Supplement #46
Review Division:	Diabetes, Lipid Disorders, and Obesity (DDLO)
Clinical Reviewers:	Mary Roberts, MD/Eileen Craig, MD
Deputy Director for Safety:	Monika Houstoun, Pharm.D., M.P.H
Division Director:	John Sharretts, MD
Review Date:	July 29, 2024
Project Manager:	Martin White

PRIOR APPROVAL SUPPLEMENT 46
Drug Interaction with Ticagrelor

The purpose of this submission is to update the Crestor Prescribing Information with the drug interaction with ticagrelor (Section 7.1 Drug Interactions that Increase the Risk of Myopathy and Rhabdomyolysis with CRESTOR and 12.3 Pharmacokinetics).

The Applicant notes that Lehtisalo et. al.[1] reported on in vitro experiments conducted to determine the effects of ticagrelor on rosuvastatin-transporting proteins, i.e., OATP1B1, OATP1B3, OATP2B1, and BCRP, in OATP-overexpressing human embryonic kidney cells and BCRP-overexpressing membrane vesicles. A static drug interaction model based on these results predicted that ticagrelor may inhibit intestinal BCRP and thus increase rosuvastatin plasma exposure 2.1-fold. A subsequent article[2] described the results of a clinical drug-drug interaction (DDI) study in 9 healthy Finnish volunteers. The authors showed a 2.6-fold increase in the AUC and Cmax of rosuvastatin, probably

[1] Lehtisalo M, Kiander W, Filppula AM, Deng F, Kidron H, Korhonen M, et al. Rhabdomyolysis during concomitant ticagrelor and rosuvastatin: a breast cancer resistance protein-mediated drug interaction? Br J Clin Pharmacol. 2023;89(7):2309-15.
[2] Lehtisalo M, Tarkiainen EK, Neuvonen M, Holmberg M, Kiiski JI, Lapatto-Reiniluoto O, et al. Ticagrelor increases exposure to the Breast Cancer Resistance Protein substrate rosuvastatin. Clin Pharmacol Ther. 2024;115(1):71-9.

due to the inhibition of intestinal BCRP. Following the results of this study, AstraZeneca completed its own in vitro study of the potential for ticagrelor to act as an inhibitor of the human efflux transporter BCRP. Based on AstraZeneca's results, ticagrelor is predicted to increase rosuvastatin plasma exposure by approximately 2-fold. (b) (4)

Additional background information for this DDI with ticagrelor includes:

- Newly Identified Safety Signal (NISS) 5120 opened on May 12, 2023, for Crestor regarding a drug interaction with ticagrelor leading to an increased risk of rhabdomyolysis. Refer to Notification of Section 921 Posting for NDA 21366 (in DARRTS 9/25/2023; Marisa Petruccelli).
- Clinical Pharmacology Memo--recommends limiting the dose of Crestor to 10 mg once daily in patients taking ticagrelor who have additional risk factors for rhabdomyolysis such as renal impairment, and age greater than 65 years (in DARRTS 5/23/2023; Hebing Liu).
- Pharmacovigilance and Epidemiology Review by Division of Pharmacovigilance I (DPV-I, Division of Epidemiology-I (DEPI-I), and Division of Epidemiology-II (DEPI-II) which provides an evaluation of the possible drug interaction between ticagrelor and rosuvastatin therapy resulting in rhabdomyolysis from the FDA Adverse Event Reporting System (FAERS) database and the medical literature and an evaluation of drug utilization data for context. This review provided evidence from FAERS, literature, pharmacokinetic studies, and clinical pharmacology studies to support the signal of a drug interaction between ticagrelor and rosuvastatin increasing the risk of rhabdomyolysis; identified risk factors were 40 mg rosuvastatin dose, advanced age, and reduced renal function. Based on the data reviewed, the recommendation was to add the interaction between rosuvastatin and ticagrelor to the labeling of both products (in DARRTS 2/14/2024; Ali Niak).
- Division of Medical Policy Programs (DMPP) Patient Labeling Review (in DARRTS 7/1/2024; Mary Carroll).
- Office of Prescription Drug Promotion (OPDP) Labeling Comments for CRESTOR (rosuvastatin calcium) tablets (in DARRTS 7/2/2024; Ankur Kalola).

Label changes for Crestor that were included in this supplement are summarized below:

- Section 1: We proposed the following revision to the current indication to better describe the overall effect of the composite endpoint and to provide consistency in labeling MACE endpoints:
    - From: To reduce the risk of stroke, myocardial infarction, and arterial revascularization procedures in adults without established coronary heart disease who are at increased risk of cardiovascular (CV) disease based on age, hsCRP ≥2 mg/L, and at least one additional CV risk factor.
    - To: To reduce the risk of major adverse cardiovascular (CV) events (CV death, nonfatal myocardial infarction, nonfatal stroke, or an arterial

revascularization procedure) in adults without established coronary heart disease who are at increased risk of CV disease based on age, high-sensitivity C-reactive protein (hsCRP) ≥2 mg/L, and at least one additional CV risk factor.
    - OPDP recommended adding the term "composite" to the indication to describe MACE as they believe that this would be helpful in addressing concerns, particularly for direct-to-consumer promotion.
    - DDLO discussed at length adding the language of "a composite endpoint of…." however, this language is not essential to inform the safe and effective use of this product in the context of the indication statement in the Prescribing Information. As is, the current indication statement is supported by substantial evidence of effectiveness and clearly and succinctly describes the data that establishes the basis of approval for this indication.
- Sections 2.1 and 2.6: Minor revisions were made.
- Section 7.1: Table 5 was modified to include drug interaction information with ticagrelor.
    - *Clinical Impact:* Concomitant use of CRESTOR and ticagrelor has been shown to increase rosuvastatin concentrations, which may result in increased risk of myopathy. Cases of myopathy and rhabdomyolysis have been reported in patients using both products concomitantly. Cases have occurred more frequently in patients taking 40 mg of rosuvastatin.
    - *Intervention:* In patients taking concomitant ticagrelor, especially those with additional risk factors for myopathy and rhabdomyolysis, monitor patients for signs and symptoms of myopathy, particularly during initiation of therapy and during upward dose titration of CRESTOR.

(b) (4)

- Section 10: Updated America's Poison Centers to current name that removes the term "control."
- Revisions were made to the patient prescribing information (PPI) for consistency with the full prescribing information (PI). Additional revisions were made to reduce redundancy, to make patient information more consistent and concise, and to include the information necessary for patients to safely take their medication.

With this submission of labeling for supplement-46 on July 29, 2024, the Applicant accepts all of FDA's most recent recommendations for labeling and submits the with revision marks (WRM) and the clean running text (CRT) of the PI.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

EILEEN M CRAIG
07/29/2024 01:38:38 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021366Orig1s046

OTHER REVIEW(S)

Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 021366 S-046

Name of Drug: Crestor (rosuvastatin calcium) tablets

Applicant: AstraZeneca Pharmaceuticals LP Agent for AstraZeneca UK Limited

Labeling Reviewed

Submission Date: May 10, 2024

Receipt Date: May 10, 2024

Background and Summary Description:
This Prior Approval labeling supplement proposes to update the Crestor Prescribing Information with the drug interaction with ticagrelor (Section 7.1 Drug Interactions that Increase the Risk of Myopathy and Rhabdomyolysis with CRESTOR and 12.3 Pharmacokinetics).

Review
This project manager compared the labeling submitted on July 29, 2024, to the currently approved version, approved with supplement 045 on July 27, 2023, using the MS Word electronic comparison function. A copy of this comparison document is appended to this review.

The following high-level changes were made to the PI and PPI:

- Revised the indication statement in Section 1 to better describe the overall effect of the composite endpoint and to provide consistency in labeling major adverse cardiovascular events (MACE) endpoints:
    - From: To reduce the risk of stroke, myocardial infarction, and arterial revascularization procedures in adults without established coronary heart disease who are at increased risk of cardiovascular (CV) disease based on age, hsCRP ≥2 mg/L, and at least one additional CV risk factor.
    - To: To reduce the risk of major adverse cardiovascular (CV) events (CV death, nonfatal myocardial infarction, nonfatal stroke, or an arterial. revascularization procedure) in adults without established coronary heart disease who are at increased risk of CV disease based on age, high-sensitivity C-reactive protein (hsCRP) ≥2 mg/L, and at least one additional CV risk factor.
- Modified Table 5 in Section 7.1 to include drug interaction information with ticagrelor.

For a full list of recommendations, please see the following reviews in DARRTS:

- Clinical Review dated July 29, 2024 (Eileen Craig, MD, Team Leader)

- Division of Medical Policy Programs (DMPP) Review dated July 1, 2024 (Mary Carroll, BSN, RN, Patient Labeling Reviewer, Lashawn Griffiths, MSHS-PH, DSH, RN, Associate Director for Patient Labeling, and Marcia Williams, PhD, Team Leader, Patient Labeling)

- Office of Prescription Drug Promotion (OPDP) Review dated July 2, 2024 (Ankur Kalolo, PharmD, Regulatory Review Officer)

Recommendations

The labeling was reviewed by Drs. Eileen Craig, Mary Roberts, Monika Houston, and Melinda Wilson and found acceptable. The supplement is ready for approval. The Agency should issue an approval letter for this supplement.

Martin White	7/30/2024
Regulatory Project Manager	Date
Liz Solomon	7/30/2024
Chief, Project Management Staff	Date

36 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MARTIN L WHITE
07/31/2024 02:55:52 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 2, 2024

To: Martin White, Regulatory Project Manager
Division of Diabetes, Lipid Disorders, and Obesity Products (DDLO)

Melinda Wilson, Associate Director for Labeling, (DDLO)

From: Ankur Kalola, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sapna Shah, Team Leader, OPDP

Subject: OPDP Labeling Comments for CRESTOR (rosuvastatin calcium) tablets, for oral use

NDA: 21366 / Supplement 46

In response to DDLO's consult request dated May 30, 2024, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for Crestor. This supplement (S46) provides for updates to the labeling regarding drug interactions with ticagrelor and the indication to reduce the risk of major cardiovascular outcomes.

PI & PPI:
OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DDLO (Martin White) on June 25, 2024, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Ankur Kalola at (301) 796-4530 or Ankur.Kalola@fda.hhs.gov.

37 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ANKUR S KALOLA
07/02/2024 09:35:20 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	July 1, 2024
To:	Martin White, M.S. Regulatory Project Manager **Division of Diabetes, Lipid Disorders, and Obesity (DDLO)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Concurrence with Submitted: Patient Package Insert (PPI)
Drug Name (established name):	CRESTOR (rosuvastatin calcium)
Dosage Form and Route:	tablets
Application Type/Number:	NDA 021366
Supplement Number:	S-046
Applicant:	AstraZeneca Pharmaceuticals, LP

1 INTRODUCTION

On May 7, 2024, AstraZeneca Pharmaceuticals, LP submitted for the Agency's review a Prior Approval Supplement (PAS) for CRESTOR (rosuvastatin calcium) tablets. The purpose of this submission is to update the CRESTOR Prescribing Information with drug interaction with ticagrelor (Section 7.1 Drug Interactions that Increase the Risk of Myopathy and Rhabdomyolysis with CRESTOR and 12.3 Pharmacokinetics).

On May 31, 2024, the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for CRESTOR (rosuvastatin calcium) tablets.

This memorandum documents the DMPP review and concurrence with the Applicant's proposed PPI for CRESTOR (rosuvastatin calcium) tablets.

2 MATERIAL REVIEWED

- Draft CRESTOR (rosuvastatin calcium) tablets PPI received on May 31, 2024, and received by DMPP on June 25, 2024.
- Draft CRESTOR (rosuvastatin calcium) tablets Prescribing Information (PI) received on May 31, 2024, revised by the Review Division throughout the review cycle, and received by DMPP on June 25, 2024.

3 CONCLUSIONS

We find the Applicant's proposed PPI is acceptable as submitted.

4 RECOMMENDATIONS

- Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARY E CARROLL
07/01/2024 02:52:24 PM

MARCIA B WILLIAMS
07/01/2024 02:53:41 PM

LASHAWN M GRIFFITHS
07/01/2024 03:20:44 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	July 1, 2024
To:	Martin White, M.S. Regulatory Project Manager **Division of Diabetes, Lipid Disorders, and Obesity (DDLO)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Mary Carroll, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Ankur Kalola, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	DMPP and OPDP Concurrence with Submitted: Patient Package Insert (PPI)
Drug Name (established name):	CRESTOR (rosuvastatin calcium)
Dosage Form and Route:	tablets
Application Type/Number:	NDA 021366
Supplement Number:	S-046
Applicant:	AstraZeneca Pharmaceuticals, LP

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This memorandum documents the DMPP and OPDP review and concurrence with the Applicant's proposed PPI for CRESTOR (rosuvastatin calcium) tablets.

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We find the Applicant's proposed PPI is acceptable as submitted.

4 RECOMMENDATIONS

- Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARY E CARROLL
07/01/2024 02:04:28 PM

MARCIA B WILLIAMS
07/01/2024 02:08:23 PM

LASHAWN M GRIFFITHS
07/01/2024 02:25:23 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021366Orig1s046

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

From: White, Martin
Sent: Tue 23 Jul 2024 07:33:51 PM -0400 UTC
To: Walsh, Sally
Subject: RE: [EXTERNAL] RE: NDA 21366/S-046 Crestor Labeling
Attachments: NDA 21366 Crestor S-46 to firm on 7.23.2024.docx

Sally,

FDA has compiled the attached comments for your draft labeling submitted for NDA 021366, supplement-046, submitted on May 10, 2024. We request that you accept all proposed changes that you agree with, make additional revisions as requested, and return a revised labeling no later than COB **July 26, 2024**.

If there are no changes, please submit the final agreed upon label to me via email. Use the SRPI checklist to ensure that the final agreed upon label conforms with format items in regulations and guidances.

Acknowledge receipt of this email and let me know if you have any questions.

Regards,
Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: Walsh, Sally <sally.walsh@astrazeneca.com>
Sent: Monday, July 22, 2024 9:13 AM
To: White, Martin <Martin.White@fda.hhs.gov>
Subject: [WARNING: ATTACHMENT(S) MAY CONTAIN MALWARE]RE: [EXTERNAL] RE: NDA 21366/S-046 Crestor Labeling

Hi Martin,

Here are the labels that have been reviewed by AstraZeneca. All FDA comments have been addressed. Please let me know if we will need to do an official submission or if email will be sufficient.

Kind regards,
Sally

Sally A. Walsh
Senior Director Regulatory Affairs
AstraZeneca

Late-stage Development, Regulatory, Cardiovascular, Renal and Metabolism (CVRM)| BioPharmaceuticals R&D
One MedImmune Way, ORD 101 3236C, Gaithersburg, MD 20878
T: +1 (301) 398-0694 M: + (b) (6)
Sally.walsh@astrazeneca.com

From: White, Martin <Martin.White@fda.hhs.gov>
Sent: Thursday, July 11, 2024 1:46 PM
To: Walsh, Sally <sally.walsh@astrazeneca.com>
Subject: RE: [EXTERNAL] RE: NDA 21366/S-046 Crestor Labeling

Sally,

FDA has compiled the attached comments for your draft labeling submitted for NDA 021366, supplement-046, submitted on May 10, 2024. We request that you accept all proposed changes that you agree with, make additional revisions as requested, and return a revised labeling no later than COB **July 22, 2024**.

If there are no changes, please submit the final agreed upon label to me via email. Use the SRPI checklist to ensure that the final agreed upon label conforms with format items in regulations and guidances.

Acknowledge receipt of this email and let me know if you have any questions.

Regards,
Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: Walsh, Sally <sally.walsh@astrazeneca.com>
Sent: Thursday, June 20, 2024 9:41 AM
To: White, Martin <Martin.White@fda.hhs.gov>
Subject: RE: [EXTERNAL] RE: NDA 21366/S-046 Crestor Labeling

Hi Martin,

Please find enclosed the clean and annotated drafts of the label. We have accepted most changes.

Do you need these submitted formally through the gateway or is email sufficient?

If you have any questions please feel free to contact me.

Kind regards,
Sally

Sally A. Walsh
Senior Director Regulatory Affairs

AstraZeneca
Late-stage Development, Regulatory, Cardiovascular, Renal and Metabolism (CVRM)| BioPharmaceuticals R&D
One MedImmune Way, ORD 101 3236C, Gaithersburg, MD 20878
T: +1 (301) 398-0694 M: + (b) (6)
Sally.walsh@astrazeneca.com

From: White, Martin <Martin.White@fda.hhs.gov>
Sent: Thursday, June 13, 2024 10:58 AM
To: Walsh, Sally <sally.walsh@astrazeneca.com>
Subject: RE: [EXTERNAL] RE: NDA 21366/S-046 Crestor Labeling

This is acceptable.

Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: Walsh, Sally <sally.walsh@astrazeneca.com>
Sent: Thursday, June 13, 2024 10:35 AM
To: White, Martin <Martin.White@fda.hhs.gov>
Subject: RE: [EXTERNAL] RE: NDA 21366/S-046 Crestor Labeling

Hi Martin,

Hope you are having a good week. We will need until the end of next week to get the label through internal approvals. Please let me know if that is okay. We will try to get it sooner if possible.

Kind regards,
Sally

Sally A. Walsh
Senior Director Regulatory Affairs

AstraZeneca
Late-stage Development, Regulatory, Cardiovascular, Renal and Metabolism (CVRM)| BioPharmaceuticals R&D
One MedImmune Way, ORD 101 3236C, Gaithersburg, MD 20878
T: +1 (301) 398-0694 M: (b) (6)
Sally.walsh@astrazeneca.com

From: White, Martin <Martin.White@fda.hhs.gov>
Sent: Friday, June 7, 2024 2:05 PM
To: Walsh, Sally <sally.walsh@astrazeneca.com>
Subject: RE: [EXTERNAL] RE: NDA 21366/S-046 Crestor Labeling

Hi Sally,

FDA has compiled the attached comments for your draft labeling submitted for NDA 021366, supplement-046, submitted on May 10, 2024. We request that you accept all proposed changes that you agree with, make additional revisions as requested, and return a revised labeling no later than COB **June 17, 2024**.

If there are no changes, please submit the final agreed upon label to me via email. Use the SRPI checklist to ensure that the final agreed upon label conforms with format items in regulations and guidances.

Acknowledge receipt of this email and let me know if you have any questions.

Thanks

Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: Walsh, Sally <sally.walsh@astrazeneca.com>
Sent: Thursday, May 30, 2024 3:44 PM
To: White, Martin <Martin.White@fda.hhs.gov>
Subject: [EXTERNAL] RE: NDA 21366/S-046

Hi Martin,

Hope you are enjoying this beautiful weather!

I acknowledge receipt.

Kind regards,
Sally

Sally A. Walsh
Senior Director Regulatory Affairs

AstraZeneca
Late-stage Development, Regulatory, Cardiovascular, Renal and Metabolism (CVRM)| BioPharmaceuticals R&D
One MedImmune Way, ORD 101 3236C, Gaithersburg, MD 20878
T: +1 (301) 398-0694 M: (b) (6)
Sally.walsh@astrazeneca.com

From: White, Martin <Martin.White@fda.hhs.gov>
Sent: Thursday, May 30, 2024 2:17 PM
To: Walsh, Sally <sally.walsh@astrazeneca.com>
Subject: NDA 21366/S-046

Hello Sally,

Attached is the Acknowledgement letter for NDA 21366/S-046.

Thanks
Martin

Martin White, MS
Regulatory Project Manager
Diabetes, Lipid Disorders, and Obesity
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.595.2123
Martin.White@fda.hhs.gov

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/s/

MARTIN L WHITE
07/24/2024 07:41:56 AM

From: White, Martin
Sent: Thu 11 Jul 2024 01:45:42 PM -0400 UTC
To: Walsh, Sally
Subject: RE: [EXTERNAL] RE: NDA 21366/S-046 Crestor Labeling
Attachments: NDA 21366 S-046 Crestor PI and PPI to firm on 7.11.2024.docx

Sally,

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Regards,
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Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: Walsh, Sally <sally.walsh@astrazeneca.com>
Sent: Thursday, June 20, 2024 9:41 AM
To: White, Martin <Martin.White@fda.hhs.gov>
Subject: RE: [EXTERNAL] RE: NDA 21366/S-046 Crestor Labeling

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Late-stage Development, Regulatory, Cardiovascular, Renal and Metabolism (CVRM)| BioPharmaceuticals R&D
One MedImmune Way, ORD 101 3236C, Gaithersburg, MD 20878
T: +1 (301) 398-0694 M: (b) (6)
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Subject: RE: [EXTERNAL] RE: NDA 21366/S-046 Crestor Labeling

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Subject: RE: [EXTERNAL] RE: NDA 21366/S-046 Crestor Labeling

Hi Sally,

FDA has compiled the attached comments for your draft labeling submitted for NDA 021366, supplement-046, submitted on May 10, 2024. We request that you accept all proposed changes that you agree with, make additional revisions as requested, and return a revised labeling no later than COB **June 17, 2024**.

If there are no changes, please submit the final agreed upon label to me via email. Use the SRPI checklist to ensure that the final agreed upon label conforms with format items in regulations and guidances.

Acknowledge receipt of this email and let me know if you have any questions.

Thanks

Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: Walsh, Sally <sally.walsh@astrazeneca.com>
Sent: Thursday, May 30, 2024 3:44 PM
To: White, Martin <Martin.White@fda.hhs.gov>
Subject: [EXTERNAL] RE: NDA 21366/S-046

Hi Martin,

Hope you are enjoying this beautiful weather!

I acknowledge receipt.

Kind regards,
Sally

Sally A. Walsh
Senior Director Regulatory Affairs

AstraZeneca
Late-stage Development, Regulatory, Cardiovascular, Renal and Metabolism (CVRM)| BioPharmaceuticals R&D

One MedImmune Way, ORD 101 3236C, Gaithersburg, MD 20878
T: +1 (301) 398-0694 M: (b) (6)
Sally.walsh@astrazeneca.com

From: White, Martin <Martin.White@fda.hhs.gov>
Sent: Thursday, May 30, 2024 2:17 PM
To: Walsh, Sally <sally.walsh@astrazeneca.com>
Subject: NDA 21366/S-046

Hello Sally,

Attached is the Acknowledgement letter for NDA 21366/S-046.

Thanks
Martin

Martin White, MS
Regulatory Project Manager
Diabetes, Lipid Disorders, and Obesity
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.595.2123
Martin.White@fda.hhs.gov

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/s/

MARTIN L WHITE
07/11/2024 02:06:23 PM

From: White, Martin
Sent: Fri 07 Jun 2024 02:05:15 PM -0400 UTC
To: Walsh, Sally
Subject: RE: [EXTERNAL] RE: NDA 21366/S-046 Crestor Labeling
Attachments: NDA 21366 S-046 track changes to firm on 6.7.2024.docx

Hi Sally,

FDA has compiled the attached comments for your draft labeling submitted for NDA 021366, supplement-046, submitted on May 10, 2024. We request that you accept all proposed changes that you agree with, make additional revisions as requested, and return a revised labeling no later than COB **June 17, 2024**.

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Thanks

Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

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Sent: Thursday, May 30, 2024 3:44 PM
To: White, Martin <Martin.White@fda.hhs.gov>
Subject: [EXTERNAL] RE: NDA 21366/S-046

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Kind regards,
Sally

Sally A. Walsh
Senior Director Regulatory Affairs
AstraZeneca

Late-stage Development, Regulatory, Cardiovascular, Renal and Metabolism (CVRM)| BioPharmaceuticals R&D
One MedImmune Way, ORD 101 3236C, Gaithersburg, MD 20878
T: +1 (301) 398-0694 M: + (b) (6)
Sally.walsh@astrazeneca.com

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Sent: Thursday, May 30, 2024 2:17 PM
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Thanks
Martin

Martin White, MS
Regulatory Project Manager
Diabetes, Lipid Disorders, and Obesity
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
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10903 New Hampshire Avenue
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Phone 240.402.6018
Fax 301.595.2123
Martin.White@fda.hhs.gov

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/s/

MARTIN L WHITE
06/10/2024 10:08:28 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-OPDP-RPM	Martin White 2404026018

REQUEST DATE:	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
5/30/2024		21366	

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Crestor	priority	statin	See below

NAME OF FIRM:	PDUFA Date: see below
AstraZeneca Pharmaceuticals LP	

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☒ PRESCRIBING INFORMATION (PI)
- ☒ PATIENT PACKAGE INSERT (PPI)
- ☐ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☐ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☒ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☒ LABELING REVISION

For OSE USE ONLY
- ☐ REMS

EDR link to submission:
Supplement 46: EDR Location: \\CDSESUB1\evsprod\NDA021366\0400

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS: DDLO received a PAS labeling supplement for NDA 21366, Crestor, to update the Prescribing Information with drug interaction with ticagrelor (Section 7.1 Drug Interactions that Increase the Risk of Myopathy and Rhabdomyolysis with CRESTOR and 12.3 Pharmacokinetics).

The Division would like to take action by late June/early July.

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one)

	☐ eMAIL ☐ HAND

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/s/

MARTIN L WHITE
05/30/2024 02:12:41 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO:

CDER-DMPP-PatientLabelingTeam

FROM: (Name/Title, Office/Division/Phone number of requestor)

REQUEST DATE:
May 30, 2024

NDA/BLA NO.
21366

TYPE OF DOCUMENTS:
(PLEASE CHECK OFF BELOW)

NAME OF DRUG:
Crestor

PRIORITY CONSIDERATION:
Priority

CLASSIFICATION OF DRUG:
Statin

DESIRED COMPLETION DATE
(Generally 2 Weeks after receiving substantially complete labeling)
See below

SPONSOR:
AstraZeneca Pharmaceuticals LP

PDUFA Date: see below

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☒ PATIENT PACKAGE INSERT (PPI)
☐ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA/ANDA
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☒ LABELING SUPPLEMENT
☐ MANUFACTURING (CMC) SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☒ LABELING REVISION

EDR link to submission:
Supplement 46: EDR Location: \\CDSESUB1\evsprod\NDA021366\0400

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS: DDLO received a PAS labeling supplement for NDA 21366, Crestor, to update the Prescribing Information with drug interaction with ticagrelor (Section 7.1 Drug Interactions that Increase the Risk of Myopathy and Rhabdomyolysis with CRESTOR and 12.3 Pharmacokinetics).

The Division would like to take action by late June/early July.

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER

Version: 06/06/2016

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/s/

MARTIN L WHITE
05/30/2024 02:14:33 PM

NDA 021366/S-046

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

AstraZeneca Pharmaceuticals LP
Agent for AstraZeneca UK Limited
Attention: Sally Walsh
Senior Regulatory Affairs Director
One MedImmune Way
Gaithersburg, MD 20878

Dear Sally Walsh:

We have received your supplemental new drug application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 021366

SUPPLEMENT NUMBER: 046

PRODUCT NAME: Crestor (rosuvastatin calcium) tablets

DATE OF SUBMISSION: May 10, 2024

DATE OF RECEIPT: May 10, 2024

This supplemental application proposes to update the Crestor Prescribing Information with drug interaction with ticagrelor (Section 7.1 Drug Interactions that Increase the Risk of Myopathy and Rhabdomyolysis with CRESTOR and 12.3 Pharmacokinetics).

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 9, 2024, in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be November 10, 2024.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i) in structured product labeling (SPL) format as described at FDA.gov.[1] Failure to submit the content of labeling in SPL format may result in a refusal-to-file action.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

If you have any questions, call me at (240) 402-6018.

Sincerely,

{See appended electronic signature page}

Martin White, M.S.
Regulatory Project Manager
Diabetes, Lipid Disorders, and Obesity
Division of Regulatory Operations for Cardiology,
Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research

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/s/

MARTIN L WHITE
05/30/2024 09:23:54 AM