



NDA 21366/S-025 and S-027

**SUPPLEMENT APPROVAL**

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

Dear Ms. DeFeo:

Please refer to your Supplemental New Drug Applications (sNDA) dated and received February 24, 2012 (S-025) and September 20, 2012 (S-027), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for CRESTOR (rosuvastatin calcium) Tablets 5 mg, 10 mg, 20 mg, and 40 mg.

We acknowledge receipt of your amendments dated March 9 (S-025), and October 24 (S-025 and S-027), 2012.

We also refer to our letter dated August 22, 2012, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for HMG-CoA reductase inhibitor (statin) drugs. This information pertains to the risk of immune-mediated necrotizing myopathy (IMNM).

Supplemental new drug application, S-027, provides for revisions to the labeling for Crestor. The agreed upon changes to the language included in our August 22, 2012, letter are as follows (additions are noted by underline and deletions are noted by ~~striketrough~~).

In the Full Prescribing Information, under **WARNINGS AND PRECAUTIONS, 5.1 Skeletal Muscle Effects**:

CRESTOR therapy should be discontinued if markedly elevated creatinine kinase levels occur or myopathy is diagnosed or suspected. CRESTOR therapy should also be temporarily withheld in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., sepsis, hypotension, dehydration, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, or uncontrolled seizures).

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with (b) (4) statin (b) (4) use. (b) (4) IMNM (b) (4) is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents.



In the Full Prescribing Information, under **ADVERSE REACTIONS, 6.3 Postmarketing Experience:**

The following adverse reactions have been identified during postapproval use of CRESTOR: arthralgia, fatal and non-fatal hepatic failure, hepatitis, jaundice, (b) (4) depression, and sleep disorders (including insomnia and nightmares). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

There have been rare reports of immune-mediated necrotizing myopathy associated with statin use [see *Warnings and Precautions (5.1)*.

In the Patient Package Insert, under **What are the Possible Side Effects of CRESTOR?**, CRESTOR can cause side effects in some people. **Serious side effects may include: Muscle Problems:**

(b) (4) If you have muscle problems that do not go away even after your health care professional has advised you to stop (b) (4) taking CRESTOR, notify your health care professional. Your health care professional may do further tests to diagnose the cause of your muscle problems.

Supplemental new drug application, S-025, provides for IMNM information and the addition of “gynecomastia” to the **ADVERSE REACTIONS**, Postmarketing Experience section of the Crestor package insert.

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

## **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert and patient package insert), with the addition of any labeling changes in pending “Changes Being Effectuated” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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

The SPL will be accessible from publicly available labeling repositories.

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

## **PROMOTIONAL MATERIALS**

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

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

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

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

**REPORTING REQUIREMENTS**

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

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

Sincerely,

*{See appended electronic signature page}*

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

ENCLOSURE:  
Content of Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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AMY G EGAN  
10/31/2012