



NDA 19766/S-077 and S-082

**SUPPLEMENT APPROVAL**

Merck Sharp & Dohme Corp.  
Attention: Carl Sparrow, Ph.D.  
Director, Worldwide Regulatory Affairs  
P.O. Box 2000, RY33-208  
Rahway, NJ 07065-0900

Dear Dr. Sparrow:

Please refer to your supplemental new drug applications dated June 12, 2009, received June 12, 2009 (S-077); and dated March 30, 2011, received March 30, 2011 (S-082), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ZOCOR (simvastatin) Tablets 10 mg, 20 mg, 40 mg, and 80 mg.

We acknowledge receipt of your amendments for S-077 dated December 9, 2009, and February 12, and October 8, 2010, and January 21, February 3, 18 and 25, March 29, April 4, May 6, 11, and June 3 (2), 2011. For supplement, S-082, we acknowledge receipt of your amendments dated April 22, May 11, 19, and June 3 (2), 2011.

We also refer to our letter dated February 28, 2011, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for ZOCOR (simvastatin). This information pertains to the risk of myopathy, including rhabdomyolysis, in patients treated with 80 mg of simvastatin based on new safety information about this risk identified since the product was approved. We also refer to our letter dated May 18, 2011 detailing the methodology and the need to submit prescription volume reports by 8 months, 14 months, 20 months, and 26 months from the date of approval of these supplements.

Supplemental new drug application, S-077, provides clinical trial data from the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Trial showing an increased risk of myopathy, including rhabdomyolysis, in patients treated with 80 mg of simvastatin versus those treated with 20 mg. Supplemental new drug application, S-082, provides for revisions to the **DOSAGE AND ADMINISTRATION**, **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, DRUG INTERACTIONS, USE IN SPECIFIC POPULATIONS**, and **CLINICAL PHARMACOLOGY** sections of the ZOCOR (simvastatin) package insert. The agreed upon changes to the labeling revisions required in our February 28, 2011 are attached in Appendix A (additions are noted by underline and deletions are noted by ~~strikethrough~~).

Supplemental new drug application, S-082, was a response to our February 28, 2011 safety labeling change notification letter.

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.

We request that the labeling approved with this letter be available on your website within 10 days of receipt of this letter.

### **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(1)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending “Changes Being 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(1)(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  
Division of Drug Marketing, Advertising, and Communications  
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 Division of Drug Marketing, Advertising, and Communications (DDMAC), 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., RPh., Regulatory Project Manager, at (301) 796-1295.

Sincerely,

*{See appended electronic signature page}*

Eric Colman, M.D.  
Deputy Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

### ENCLOSURE(S):

Appendix A: Agreed upon changes to labeling revisions  
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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ERIC C COLMAN  
06/08/2011