DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21687/S-046 and S-047

SUPPLEMENT APPROVAL

MSD International GmbH
Attention: Catherine Kohler, Pharm.D, Agent
Director, Regulatory Affairs
Merck Sharp & Dohme Corp.
P.O. Box 1000, UG2CD-48
North Wales, PA 19454-1099

Dear Dr. Kohler:

Please refer to your Supplemental New Drug Applications (sNDA) dated and received July 18, 2012 (S-046) and September 20, 2012 (S-047), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VYTORIN (ezetimibe/simvastatin) Tablets 10/10 mg, 10/20 mg, 10/40 mg and 10/80 mg.

We acknowledge receipt of your amendment dated October 24, 2012 (S-046 and S-047).

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-047, provides for revisions to the labeling for Vytorin. 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 ~~strikethrough~~).

In the Full Prescribing Information, under **WARNINGS AND PRECAUTIONS, 5.1 Myopathy/Rhabdomyolysis**:

> There have been rare reports of ~~i~~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.
>
> (b) (4)

(b) (4)

In the Full Prescribing Information, under **ADVERSE REACTIONS, 6.2 Post-Marketing Experience**:

> The following adverse reactions have been reported in post-marketing experience for VYTORIN or ezetimibe or simvastatin: pruritus; alopecia; erythema multiforme; a variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails); dizziness; muscle cramps; myalgia; arthralgia; pancreatitis; paresthesia; peripheral neuropathy; vomiting; nausea; anemia; erectile dysfunction; interstitial lung disease; myopathy/rhabdomyolysis (b) (4) ~~*[see Warnings and Precautions (5.1)]*~~; hepatitis/jaundice; fatal and non-fatal hepatic failure; depression; cholelithiasis; cholecystitis; thrombocytopenia; elevations in liver transaminases; elevated creatine phosphokinase.
>
> 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 should tell my doctor before and while taking VYTORIN?**,

> **Tell your doctor right away if you have unexplained muscle pain, tenderness, or weakness especially with fever while you take VYTORIN. Muscle problems, including muscle breakdown, can be serious in some people and rarely cause kidney damage that can lead to death.**
>
> The risk of muscle breakdown is greater at higher doses of VYTORIN, particularly the 10/80 mg dose.
>
> The risk of muscle breakdown is greater in people 65 years of age and older, females, and people with kidney or thyroid problems.
>
> (b) (4) If you have muscle problems that do not go away even after your doctor has advised you to stop (b) (4) taking VYTORIN, notify your doctor. Your doctor may do further tests to diagnose the cause of your muscle problems.

Supplemental new drug application, S-046, provides information regarding the concomitant use of Vytorin and dronedarone, the co-administration of Vytorin with voriconazole and updated information on the use of grapefruit juice to the package insert for Vytorin.

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 Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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

The SPL will be accessible from publicly available labeling repositories.

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

PROMOTIONAL MATERIALS

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

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

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

promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.
All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

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

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

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Content of Labeling

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

/s/

AMY G EGAN
10/31/2012