DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 19898/S-063 and S-064

SUPPLEMENT APPROVAL

Bristol-Myers Squibb Company
Attention: Ana Ma. Cibrian
Director, GRS Mature Products
P.O. Box 4000
Princeton, N.J. 08543

Dear Ms. Cibrian:

Please refer to your Supplemental New Drug Applications (sNDA) dated and received September 21, 2012, for S-063 and S-064, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for PRAVACHOL (pravastatin sodium) Tablets 10 mg, 20 mg, 40 mg, and 80 mg.

We acknowledge receipt of your amendment dated October 26, 2012 (S-063 and S-064).

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-063, provides for revisions to the labeling for Pravachol. 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~~).

On the Highlights page, under **WARNINGS AND PRECAUTIONS**:

> Skeletal muscle effects (e.g., myopathy and rhabdomyolysis): predisposing factors include advanced age (~~>~~≥65), uncontrolled hypothyroidism, and renal impairment. Patients should be advised to ~~report~~ promptly report to their physician any unexplained and/or persistent muscle pain, tenderness, or weakness. Pravastatin therapy should be discontinued if myopathy is diagnosed or suspected. (5.1, 8.5)

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

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 CPK, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents.

(b) (4)

All patients should be advised to ~~report~~ promptly report to their physician unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing PRAVACHOL.

In the Full Prescribing Information, under **ADVERSE REACTIONS, 6.2 Postmarketing Experience**, *Musculoskeletal*:

myopathy, rhabdomyolysis~~.~~ (b) (4)

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

Supplemental new drug application, S-064, provides for the addition of information regarding the concomitant use of Pravachol and boceprevir to the package insert for Pravachol. This information was submitted in response to our September 13, 2012, prior approval supplement request 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.

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