DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20903/S-050
NDA 21546/S-006

SUPPLEMENT APPROVAL
LABELING REBUTTAL ACCEPTED

Merck Sharp & Dohme Corp.
Attention: Ursula Marek, Pharm.D.
Associate Director, Global Regulatory Affairs
2015 Galloping Hill Road, K-15-3
Kenilworth, NJ 07033

Dear Dr. Marek:

Please refer to your Supplemental New Drug Applications (sNDAs) dated November 28 and December 7, 2012 , received November 28 and December 7, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for REBETOL® (ribavirin) 200 mg Capsules (NDA 20903) and 40 mg per mL Oral Solution (NDA 21546).

We acknowledge receipt of your amendments dated December 12, 2012 and January 28, 2013.

On October 29, 2012, we sent you a letter invoking our authority under section 505(o)(4) of the FDCA to require safety related label changes to the labeling of REBETOL® (ribavirin) to address new information about the occurrence of the ribavirin-associated substitution, NS5B_F415Y, in hepatitis C (HCV) genotype 1a patients who fail combination HCV ribavirin-containing treatment regimens. The decision to require safety labeling changes was based on new safety information about this risk identified since this product was approved, which consists of review of published scientific literature (Young et al., 2003; Ward et al., 2008; and Bartels et al., 2011[1,2,3]). You were directed to submit, within 30 days of the date of that letter, a supplement proposing changes to the approved labeling, or to notify FDA that you do not believe a labeling change is warranted, and submit a rebuttal statement detailing the reasons why such a change is not warranted.

We acknowledge receipt of your rebuttal statement dated November 28, 2012 detailing the reasons why you believe a labeling change to address the new resistance information is not warranted for REBETOL® (ribavirin).

We have completed the review of your rebuttal statement. We do not agree with your statement that the clinical significance of the NS5B_F415Y substitution is unknown at this time. We believe that the ribavirin-associated substitution may have an impact on drugs currently under development (see Bartels et al.). However, because there are no HCV NS5B polymerase inhibitors currently marketed, we agree that no labeling change is warranted at this time to address the new resistance information described above.

Additionally, you provided the following revision to the Package Insert:

> Deletion of reference to ribavirin as a potential carcinogen in the NONCLINICAL TOXICOLOGY, Carcinogenesis, Mutagenesis, Impairment of Fertility, Carcinogenesis sub-section.

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), 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.

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 Kyong Hyon, Safety Regulatory Project Manager, at (301) 796-0734.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, M.D.
Deputy Director of Safety
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling

[1] Young K.-C., Lindsay K.L., Lee K.-J., Liu W.-C, He J.-W., Milstein S.L., and Lai M.C. (2003). Identification of a Ribavirin-Resistant NSSB Mutation of Hepatitis C Virus during Ribavirin Monotherapy. Hepatology 38: 869-878.

[2] Ward C.L., Rigby S., Symonds W.T., Patel K., Zekry A., Pawlotsky J.M., and McHutchison J.G. (2008). Interferon and Ribavirin Therapy Does Not Select for Resistance Mutations in Hepatitis C Virus Polymerase. J Viral Hepat. 15(8):571-7.

[3] Bartels D.J., Tigges A.M., Sullivan J.C., Henshaw J., Jiang M., Zhang E.Z., Dorrian J., Kwong A.D., and Kieffer T.L. (2011). Enrichment of the NS5B Polymerase Variant F415Y Following Failure of Ribavirin Containing Regimens in Patients with Subtype 1a HCV. 6th International Workshop on Hepatitis C - Resistance & New Compounds, Boston, MA. June 23-24, 2011.

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/s/

KENDALL A MARCUS
02/06/2013