



NDA 22145/S-026  
NDA 203045/S-003

**SUPPLEMENT APPROVAL**

Merck Sharp & Dohme Corp.  
Attention: Robert A. Fromtling, Ph.D.  
Director, Worldwide Regulatory Affairs  
126 E. Lincoln Avenue  
P.O. Box 2000, RY 33-212  
Rahway, NJ 07065-0900

Dear Dr. Fromtling:

Please refer to your Supplemental New Drug Applications (sNDAs) dated July 13, 2012, received July 13, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Isentress® (raltegravir) 400 mg film-coated tablets (NDA 22145) and 100 mg scored and 25 mg chewable tablets (NDA 203045).

We acknowledge receipt of your amendments dated July 30, 2012.

We also refer to our letter dated June 14, 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 antiretroviral products. This information pertains to the risk of the autoimmune disorder as syndromes that can occur in the setting of immune reconstitution with the use of antiretroviral products.

These supplemental new drug applications provide for revisions to the labeling for Isentress® (raltegravir) 400 mg film-coated tablets (NDA 22145) and 100 mg scored and 25 mg chewable tablets (NDA 203045), consistent with our June 14, 2012 letter as follows (additions are noted by underline and deletions are noted by ~~strikethrough~~).

1. The **RECENT MAJOR CHANGES** in the **HIGHLIGHTS** section of the label has been revised as follows:

-----**RECENT MAJOR CHANGES**-----

Indications And Usage (1)	12/2011
Indications And Usage (1)	04/2012
Dosage And Administration (2)	12/2011
Warnings And Precautions (5.1)	11/2011
Warnings And Precautions (5.2)	<del>XX/XXXX</del>
Warnings And Precautions (5.3)	12/2011

2. The revision date has been changed from 4/2012 to XX/XXXX at the end of the **HIGHLIGHTS** section of the label.
3. The **WARNINGS AND PRECAUTIONS/Immune Reconstitution Syndrome** subsection has been revised as follows:

~~During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* complex, cytomegalovirus, *Pneumocystis jiroveci* pneumonia, *Mycobacterium tuberculosis*, or reactivation of varicella zoster virus), which may necessitate further evaluation and treatment. Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including ISENTRESS.~~  
During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jiroveci* pneumonia, tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment.

4. The fourth sentence of the second paragraph in the **PATIENT COUNSELING INFORMATION** has been revised as follows:

Patients should be advised to continue to practice safer sex and to use latex or polyurethane condoms ~~or other barrier methods~~ to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions or blood.

5. **Patient Information Labeling:**

- a. The end of patient package insert has been revised as follows:

~~USPI-T-05181204R019~~

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U.S. Patent Nos. US 7,169,780

6. USPI-T-05181207 has been placed at the left corner of each page.

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, text for the Medication Guide), 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, MD  
Deputy Director for Safety  
Division of Antiviral Products  
Office Antimicrobial Products  
Center for Drug Evaluation and Research

ENCLOSURE(S):  
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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KENDALL A MARCUS  
08/10/2012