

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-145

APPROVAL LETTER



NDA 22-145

Merck & Co., Inc.
Attention: Robert A. Fromtling, Ph.D.
Director, Worldwide Regulatory Affairs
126 E. Lincoln Avenue
P.O. Box 2000, RY33-208
Rahway, NJ 07065-0900

Dear Dr. Fromtling:

Please refer to your new drug application (NDA) 22-145 dated April 13, 2007, received April 13, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Isentress™ (raltegravir) 400 mg tablets.

We acknowledge receipt of your submissions dated:

| | | | |
|-------------------|-------------------|---------------------|------------------------|
| January 12, 2007 | June 13, 2007 | August 1, 2007 (2) | September 7, 2007 |
| January 31, 2007 | June 15, 2007 | August 3, 2007 (2) | September 12, 2007 |
| February 27, 2007 | June 22, 2007 | August 6, 2007 | September 13, 2007 |
| March 15, 2007 | June 26, 2007 | August 7, 2007 | September 17, 2007 (2) |
| April 30, 2007 | July 2, 2007 | August 8, 2007 | September 18, 2007 |
| May 11, 2007 (2) | July 9, 2007 | August 9, 2007 | September 19, 2007 |
| May 15, 2007 (2) | July 10, 2007 | August 10, 2007 (2) | September 20, 2007 |
| May 18, 2007 | July 20, 2007 (3) | August 16, 2007 (2) | September 21, 2007 |
| May 24, 2007 | July 23, 2007 (2) | August 17, 2007 | September 21, 2007 |
| May 31, 2007 | July 25, 2007 | August 20, 2007 | September 25, 2007 |
| June 4, 2007 | July 26, 2007 (3) | August 21, 2007 (2) | October 3, 2007 |
| June 7, 2007 | July 27, 2007 | August 29, 2007 | October 8, 2007 |
| June 11, 2007 | July 31, 2007 | August 30, 2007 | October 9, 2007 |

This new drug application provides for the use of Isentress™ (raltegravir) 400 mg tablets in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.

We completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.510), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text (package insert, patient package insert, immediate container label). Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed agreed-upon labeling text (package insert, patient package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 22-145."

Please submit final printed container label that is identical to the enclosed immediate container label as soon as it is available, but no more than 30 days after it is printed. Please submit this label electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005). Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "Final Printed Container Label for approved NDA 22-145." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. We note that the following postmarketing study commitment specified in your submission dated October 8, 2007 was agreed-upon during a teleconference held on October 5, 2007. This commitment, along with the agreed-upon completion date is listed below:

1. By December 31, 2008, submit study reports for Week 48 data analyses for the ongoing Phase 3 Studies 018 and 019.

Please submit final study reports to NDA 22-145 as a supplemental application. For administrative purposes, all submissions relating to this postmarketing study commitment must be clearly designated "**Subpart H Postmarketing Study Commitment.**"

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your studies in pediatric subjects from 4 weeks to 18 years of age until June 30, 2011. We are waiving submission of your studies in pediatric subjects from birth up to 4 weeks of age (neonates) because the number of neonates diagnosed with HIV-1 infection is very small; therefore, there are too few pediatric subjects to study in this age group with this disease.

Your deferred pediatric studies required under Section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81. We note the following postmarketing study commitments specified in your submission dated October 8, 2007, that were agreed-upon during a teleconference held on October 5, 2007. These commitments, along with the agreed-upon completion dates are listed below:

2. Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric subjects from 2 to 18 years of age. This study will determine raltegravir exposure (pharmacokinetic profile) followed by 24 weeks of dosing. Efficacy will be based on viral load reduction through 24 weeks of dosing and safety will be monitored for a minimum of 24 weeks to support raltegravir dose selection, safety, and efficacy in this population.

Protocol Submission Date: Ongoing

Final Study Report Submission Date: June 30, 2011

3. Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric subjects from 4 weeks to 2 years of age. This study will determine raltegravir exposure (pharmacokinetic profile) followed by 24 weeks of dosing. Efficacy will be based on viral load reduction through 24 weeks of dosing and safety will be monitored for a minimum of 24 weeks to support raltegravir dose selection, safety, and efficacy in this population.

Protocol Submission Date: September 30, 2008

Final Study Report Submission Date: June 30, 2011

Please submit final study reports to NDA 22-145. For administrative purposes, all submissions related to these pediatric postmarketing study commitments must be clearly designated **“Required Pediatric Study commitments.”**

In addition, we note the following postmarketing study commitments, specified in your submission dated October 8, 2007, that were agreed-upon during a teleconference held on October 5, 2007, and are not a condition of the accelerated approval regulations. These commitments, along with the agreed-upon completion dates are listed below:

Clinical

4. Submit Week 96 report and datasets for Protocols 018 and 019.

Protocol Submission Date: Completed

Week 96 Report and Datasets Submission Date: December 31, 2009

5. Conduct a five-year follow-up for subjects in Protocols 018 and 019 focusing on safety evaluations, which should include but not be limited to assessment of mortality, malignancy, herpes zoster, creatine kinase elevations, and other adverse events.

Protocol Submission Date: May 31, 2008

Final Study Report Submission Date: December 31, 2012

6. Submit Week 48 report and datasets for Protocol 021.

Protocol Submission Date: Completed

Week 48 Report and Datasets Submission Date: March 31, 2009

7. Conduct a non-interventional, prospective, observational study to provide additional safety data on important clinical events. The duration of the study will be 5 years from initiation of the study; data will be reviewed on an interim basis every 6 months during the course of the study.

Protocol Submission Date: March 31, 2008

Final Study Report Submission Date: December 31, 2014

Pharmacology/Toxicology

8. Complete the ongoing carcinogenicity study in mice and submit the final report.

Protocol Submission Date: Completed

Final Study Report Submission Date: July 25, 2008

9. Complete the ongoing carcinogenicity study in rats and submit the final report.

Protocol Submission Date: Completed

Final Study Report Submission Date: August 15, 2008

Microbiology

10. Determine the susceptibility in cell culture of HIV-1 harboring Y143C/H/R individually and in combination with L74M, E92Q, T97A, G163R, and S230R in a common genetic background.

Protocol Submission Date: December 31, 2007

Final Study Report Submission Date: September 30, 2008

11. Evaluate the contributions of L74M/R, T97A, V151I, G163R, H183P, Y226C/D/F/H, and S230N/R substitutions to raltegravir resistance by site-directed mutagenesis.

Protocol Submission Date: December 31, 2007

Final Study Report Submission Date: September 30, 2008

Special Populations

12. Conduct a 48-week, open-label, non-randomized, single arm, diversity cohort study in 200 HIV-positive patients to assess efficacy and safety. At least 50% of the total enrollment will be African American patients and at least 25% of the total enrollment will be female patients in order to characterize the efficacy and safety of raltegravir in a population that closely reflects the United States HIV-1 infected patient population.

Protocol Submission Date: July 31, 2008

Final Study Report Submission Date: March 31, 2012

Clinical Pharmacology

13. Conduct an in vitro study (e.g., in human hepatocytes) to evaluate the relative UGT1A1 induction potency of phenytoin, phenobarbital, rifabutin, and rifampin using raltegravir as a probe substrate.

Protocol Submission: December 31, 2007

Final Report Submission: November 30, 2008

14. Conduct an in vitro study (e.g., in human hepatocytes) to evaluate the potential of raltegravir to induce CYP1A2 and CYP2B6.

Protocol Submission: December 31, 2007

Final Report Submission: November 30, 2008

Please submit clinical protocols to your IND for this product. Please submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to NDA 22-145. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to NDA 22-145. The status summary should include expected summary report and final report submission dates, any changes in plans since the last annual report, and for clinical studies, the number of patients enrolled in each study. All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled **“Postmarketing Study Commitment Protocol”, Postmarketing Study Commitment Final Report” or “Postmarketing Study Commitment Correspondence.”**

The following are **not** postmarketing study commitments; however, we note that they are specified in your submission dated October 8, 2007, that were agreed-upon in a teleconference held on October 5, 2007; these are listed below:

Microbiology

1. Perform genotypic and phenotypic analyses of HIV-1 from patients who experience virologic failure to raltegravir (plus OBT) therapy out to 48 and 96 weeks in ongoing clinical trials.
2. Contact leading investigators studying RAG1/2 recombinase in a timely fashion about conducting studies to evaluate raltegravir’s potential for inhibiting RAG1/2, and provide raltegravir to interested researchers.
3. Characterize phenotypically and genotypically virus selected in cell culture for resistance to raltegravir using distantly related non-clade B HIV-1 isolates.

Protocol Submission Date: December 31, 2007

Final Study Report Submission Date: December 31, 2009

Clinical Pharmacology

4. Submit final study reports of the UGT1A1 polymorphism study, the rifampin plus 800 mg raltegravir study, and the omeprazole-raltegravir drug interaction study.

5. Conduct a drug interaction study of rifabutin and raltegravir.

As required by 21 CFR 314.550, please submit all promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement. Please send two copies of all promotional materials directly 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

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

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

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, please call Monica Zeballos, Pharm.D., Senior Regulatory Project Manager, at (301) 796-0840.

Sincerely yours,

{See appended electronic signature page}

Edward Cox, M.D., M.P.H.
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

Enclosures: Approved draft package insert (PI), patient package insert (PPI), and immediate container label

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

/s/

Edward Cox

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