



NDA 20-628/S-33
NDA 21-785/S-10

SUPPLEMENT APPROVAL

Hoffmann-La Roche, Incorporated
Attention: Barbara S. Taylor, Ph.D.
Director, Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Dr. Taylor:

Please refer to your Supplemental New Drug Applications (sNDA) dated April 2, 2010, received April 5, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for INVIRASE® (saquinavir mesylate), 200 mg capsules and 500 mg film-coated tablets.

We acknowledge receipt of your amendments dated May 5, 2010, June 18, 2010, August 23, 2010, August 30, 2010, September 10, 2010, September 17, 2010, September 21, and October 4, 2010.

These “Prior Approval” supplemental new drug applications were submitted to convert the Patient Package Insert to a Medication Guide, to convert the USPI to PLR format and to update the label with the following changes:

- Inclusion in the Contraindications, WARNINGS and PRECAUTIONS, Drug Interactions and Clinical Pharmacology sections of the USPI of the effects of INVIRASE/ritonavir on QT and PR interval prolongation. This includes contraindicating use with certain drugs due to potentially life-threatening cardiac arrhythmias and updating the Clinical Pharmacology section with the results of an adequate QT study in healthy volunteers.
- The addition in the Drug Interactions section of the results of a study with rifabutin, addition of a statement recommending dose reduction of the rifabutin when used in combination with INVIRASE/ritonavir, and increased monitoring for adverse events and for concentrations of rifabutin to ensure adequate exposure.
- Inclusion in the Use in Specific Populations section of a statement that no dose adjustment is necessary for HIV-infected patients with mild or moderate hepatic impairment.
- To update the Adverse Reactions section of the label.

We have completed our review of these supplemental applications, as amended. The applications 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, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the patient package insert, Medication Guide) and include the labeling changes proposed in any pending “Changes Being Effectuated” (CBE) supplements. 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 pending “Changes Being Effectuated” (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.

IMMEDIATE CONTAINER LABELS

Submit final printed container labels that are identical to the labels submitted on September 21, 2010 (200 mg Capsules) and September 28, 2010 (500 mg Film-Coated Tablets) except with the revisions listed below, as soon as they are available, but no more than 30 days after they are printed.

- Please change the color of the Medication Guide language on the container from red to black.

“Attention Pharmacist: Dispense the attached Medication Guide to each patient. Do not cover Alert box with pharmacy label.”

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. The details of the REMS requirements were outlined in our REMS notification letter dated May 21, 2010.

Since INVIRASE (saquinavir mesylate) was approved on December 17, 2004 (tablets) and December 6, 1995 (capsules), we have become aware of reported electrocardiogram changes in the QTc and PR intervals associated with the use of INVIRASE (saquinavir mesylate), thus putting certain patients at increased risk for cardiac arrhythmias. We consider this information to be “new safety information” as defined in section 505-1(b) of FDCA.

Your proposed REMS, submitted on September 21, 2010, and appended to this letter, is approved. The REMS consists of the Medication Guide included with this letter and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include, but is not limited to, an evaluation of patients’ understanding of the serious risks of INVIRASE (saquinavir mesylate).

Assessments of an approved REMS must include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

If you currently distribute or plan to distribute an authorized generic product under this NDA, you will also need to submit a REMS, REMS supporting document, and any required appended documents for that authorized generic, to this NDA. In other words, you must submit a complete proposed REMS that relates only to the authorized generic product. Review and approval of the REMS is required before you may market your product.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 20-628 or 20-785 REMS ASSESSMENT

**NEW SUPPLEMENT FOR NDA 20-628 or 21-785
PROPOSED REMS MODIFICATION
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 20-628 or 21-785
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIAL

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
Division of Drug Marketing, Advertising, and Communications
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(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 Division of Drug Marketing, Advertising, and Communications (DDMAC), 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.

LETTERS TO HEALTH CARE PROFESSIONALS

Please submit your “Dear Health Care Professional” letter, at least 24 hours prior to issuing the letter; an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

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 Patricia Hong, Regulatory Project Manager, at (301) 796-0807 or 301-796-1500.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products,
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Content of Labeling
Container Labeling
REMS

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

/s/

KENDALL A MARCUS
10/06/2010