DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20628/S-038
NDA 21785/S-015

SUPPLEMENT APPROVAL

Hoffmann-La Roche Inc. c/o Genentech, Inc.
Attention: Michelle H. Rohrer, Ph.D.
Vice President, Regulatory Affairs
1 DNA Way
South San Francisco, CA
94080-4990

Dear Dr. Rohrer:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received November 18, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Invirase® (saquinavir mesylate) , 200 mg Capsules (NDA 20628) and 500 mg Tablets (NDA 21785).

We acknowledge receipt of your amendments dated January 5, 2012 in response to our General Advice letter dated, December 12, 2011.

We also refer to our letter dated October 19, 2011, 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.

In addition, we refer to non-safety labeling changes in our October 19, 2011 letter for all antiretroviral products based on recent studies demonstrating decreased transmission of HIV when HIV-infected patients or their uninfected partners take antiretroviral medication.

These supplemental new drug applications provide for revisions to the labeling for Invirase® (saquinavir mesylate), 200 mg Capsules (NDA 20628) and 500 mg Tablets (NDA 21785), consistent with our October 19 and December 12, 2011 letters, as follows (additions are noted by underline and deletions are noted by ~~strikethrough)~~.

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

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

~~Indications and Usage 10/2010~~
~~Contraindications (4) 10/2010~~

~~Warnings and Precautions, PR Interval Prolongation (5.2) 10/2010~~
~~Warnings and Precautions, QT Interval Prolongation (5.3) 10/2010~~
Warnings and Precautions (5.10) mm/yyyy

2. The word, "breast-feed" has been revised to "breastfeed" throughout the labeling.

3. Invirase has been revised to INVIRASE throughout the labeling.

4. The revision date has been changed from 10/2010 to mm/yyyy at the end of the **HIGHLIGHTS** section.

5. The second paragraph of the INDICATIONS AND USAGE section in the FULL PRESCRIBING INFORMATION has been revised as follows:

   The following points should be considered when initiating therapy with INVIRASE:
   - The twice daily administration of INVIRASE in combination with ritonavir is supported by safety data from the MaxCmin 1 study *[see Adverse Reactions (~~6.2~~6.1)]* and pharmacokinetic data *[see Clinical Pharmacology (12.3)]*.
   - The efficacy of INVIRASE with ritonavir has not been compared against the efficacy of antiretroviral regimens currently considered standard of care.
   - The number of baseline primary protease inhibitor mutations affects the virologic response to INVIRASE/ritonavir.

6. The **WARNINGS AND PRECAUTIONS/Immune Reconstitution Syndrome** sub-section has been revised as follows:

   Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including INVIRASE. 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 jirovecii* pneumonia (PCP), or 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.

7. The **DRUG INTERACTIONS**/7.3 Established and Other Potentially Significant Drug Interactions section has been revised as follows:

   Table 3: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interactions with INVIRASE/ritonavir

Concomitant Drug Class: ***Specific Drugs***	**Effect on Concentration of Atazanavir or Concomitant Drug**	**Clinical Comment**
HIV-1 protease inhibitor: Atazanavir[a]	**INVIRASE/ritonavir** ↑ Saquinavir ↑ Ritonavir ↔ Atazanavir	Atazanavir in combination with INVIRASE/ritonavir should be used with caution. Additive effects on PR interval prolongation may occur with INVIRASE/ritonavir *[see Warnings and Precautions (~~5.10~~5.2)]*.
	Other Agents	
HMG-CoA reductase inhibitors[b]*:* Aa~~a~~torvastatin, ~~rosuvastatin~~	↑ Aa~~a~~torvastatin ~~↑ rosuvastatin~~	Titrate atorvastatin dose carefully and use the lowest dose necessary; do not exceed atorvastatin 20 mg/day. ~~Use lowest possible dose of atorvastatin or rosuvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as fluvastatin in combination with Invirase/ritonavir.~~

[a]See **Drug Interactions (7)**, **Table 5~~6~~** and **Table 6~~7~~** for magnitude of interactions.
[b]INVIRASE/ritonavir interaction has not been evaluated.

8. The word, "Cmax" has been revised to "C_{max}" in the fourth sentence of the first paragraph in the **12.2. Pharmacodynamics** section of the labeling.

9. The Table 5 reference has been revised as Table 4 in the third paragraph of the 12.3 **Pharmacokinetics/**Absorption and Bioavailability in Adults section of the labeling.

10. The reference, "[*see Warnings and Precautions (5)]"* has been revised as "[*see Warnings and Precautions (5.5)]"* in the **Pharmacokinetics/**Special Populations/*Hepatic Impairment* sub-section of the labeling.

11. The **Pharmacokinetics/**Drug Interactions sub-section of the labeling has been revised as follows:

    ~~Table 6~~**Table 5** summarizes the effect of saquinavir soft gel capsules and INVIRASE with and without ritonavir on the geometric mean AUC and C_{max} of coadministered drugs. ~~Table 7~~ **Table 6** summarizes the effect of coadministered drugs on the geometric mean AUC and C_{max} of saquinavir.

12. The second paragraph of the **PATIENT COUNSELING INFORMATION** section has been revised as follows:

~~Patients should be informed that INVIRASE is not a cure for HIV-1 infection and that they may continue to acquire illnesses associated with advanced HIV-1 infection, including opportunistic infections. They should be informed that INVIRASE therapy has not been shown to reduce the risk of transmitting HIV-1 to others through sexual contact or blood contamination.~~ INVIRASE is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using INVIRASE.

Patients should be advised to avoid doing things that can spread HIV-1 infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom ~~or other barrier method~~ to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** We do not know if INVIRASE can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

13. **Medication Guide**:

a. The sixth bulleted paragraph in the "**What should I tell my healthcare provider before taking INVIRASE?**" section has been revised as follows:
   - are breast-feeding or plan to breastfeed. ~~It is not known if INVIRASE passes into your breast milk. You should not breastfeed if you are taking INVIRASE. If you are a woman who has or will have a baby while taking INVIRASE, talk with your healthcare provider about the best way to feed your baby. The Centers for Disease Control and Prevention (CDC) recommends that HIV-infected mothers not breastfeed to avoid the risk of passing HIV infection to your baby.~~ **Do not breastfeed.** We do not know if INVIRASE can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

b. Rosuvastatin (CRESTOR®) was removed from the list of drugs to be monitored closely in the "Your Healthcare provider may need to monitor your therapy more closely if you take INVIRASE and NORVIR with the following medicines" section.

c. The first paragraph of the **General information about INVIRASE** section has been revised as follows: ~~INVIRASE does not cure HIV, and it does not prevent you from getting other illness from advanced HIV infections. INVIRASE does not stop you from passing HIV infections to others. Do not share needles, or personal items that can have blood or body fluids on them, like toothbrushes and razor blades. Always practice safer sex by using condoms to lower the chance of sexual contact with semen, vaginal secretions, or blood.~~ (b) (4)

[redacted](b) (4) INVIRASE is not a cure for HIV-1 infection and you may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. You should remain under the care of a doctor when using INVIRASE.

Avoid doing things that can spread HIV-1 infection.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom ~~or other barrier method~~ to lower the chance of sexual contact with semen, vaginal secretions, or blood.

14. The end section of the labeling has been revised as follows:

~~IET_318959_PI_042010_K~~ IETC_318959_PI_2011_05_K

~~IEC_318959_PI_042010_N~~

~~IET_318959_MG_062010_K~~ IETC_318959_MG_2011_05_K

~~IEC_318959_MG_062010_N~~

Revised: ~~10/2010~~Month Year

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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

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
02/17/2012