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APPLICATION NUMBER:

21-785

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN
SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-785

Hoffman-La Roche
Attention: Matthew Lamb, Pharm.D.,
Senior Program Manager Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Dr. Lamb:

Please refer to your new drug application (NDA) dated June 17, 2004, received June 18, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Invirase® (saquinavir mesylate) 500 mg film coated tablet.

We acknowledge receipt of your submissions dated August 12, 2004, August 20, 2004, August 24, 2004, September 21, 2004, September 23, 2004, September 24, 2004 (2), November 2, 2004, November 3, 2004, November 5, 2004, November 10, 2004, December 6, 2004 (2) and December 7, 2004.

This new drug application provides for the use of Invirase® (saquinavir mesylate) 500 mg film coated tablets in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and text for the patient package insert submitted December 16, 2004 and immediate container label submitted December 6, 2004). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and a unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this **"FPL for approved NDA 21-785."** Approval of this submission by FDA is not required before the labeling is used.

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 pediatric studies for ages 4 months to adolescence until March 31, 2006.

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. This commitment is listed below.

1. Deferred pediatric studies under PREA for the treatment of HIV infection in combination with other antiretroviral agents in pediatric patients ages 4 months to adolescence.

Timeframe for submission = On or before March 31, 2006

Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated **“Required Pediatric Study Commitments.”**

In addition, we note your following postmarketing study commitments as specified in your submission dated December 6, 2004. These commitments are listed below.

2. Conduct a retrospective analysis on the effects of gender on the safety profile of SQV 1000 mg/RTV 100 mg. Safety data should be provided from at least 50 to 100 female participants with appropriately matched comparative data from male subjects.

Timeframe for submission = On or before December 17, 2005

3. Conduct a safety analysis by gender and saquinavir levels for subjects who received SQV 1000 mg/RTV 100 mg and were enrolled in the pharmacokinetic substudies of the MaxCmin 1 and MaxCmin 2 studies. Data from the two studies should be pooled for analysis and a uniform adverse event coding system should be used.

Timeframe for submission = On or before December 17, 2005

4. Determine the baseline genotype of all PI-experienced responders in the MaxCmin 1 and MaxCmin 2 studies and submit in the resistance template format. Resubmit MaxCmin 1 and MaxCmin 2 failure dataset with a column identifying isolate (specifically “baseline”) and with a column identifying outcome (nonresponder, rebound, censored, etc.)

Timeframe for submission = On or before June 17, 2005

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. 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 this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual

report, and for clinical studies, number of patients entered in to each study. All submissions, including supplements, related to these postmarketing study commitments must be prominently labeled **“Postmarketing study Protocol”, Postmarketing Study Final Report”, or “Postmarketing Study Correspondence.”**

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Antiviral Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

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

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 Kenny Shade, JD, BSN, Regulatory Project Manager, at (301)827-2335.

Sincerely,

{See appended electronic signature page}

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

Enclosure

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

/s/

Debra Birnkrant
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NDA 21-785