



NDA 21-481/S-002

Hoffmann-La Roche, Inc.
Attention: Natasha Jarrett, Director, Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Ms. Jarrett:

Please refer to your supplemental new drug application dated December 12, 2003, received December 15, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fuzeon[®] (enfuvirtide) for injection, 90 mg.

We acknowledge receipt of your submissions dated January 22, 2004, April 29, 2004, October 13, 2004, and October 14, 2004.

This supplemental new drug application provides for the use of Fuzeon[®] (enfuvirtide) for injection, in combination with other antiretroviral agents, for the treatment of HIV-1 infection in treatment experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy.

We completed our review of this application, as amended. This application 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, text for the patient package insert).

Please submit the FPL electronically 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, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-481/S-002." Approval of this submission by FDA is not required before the labeling is used.

We approved this NDA under the regulations at 21 CFR 314 Subpart H for accelerated approval of new drugs for serious or life-threatening illnesses. Approval of this supplement fulfills your commitments made under 21 CFR 314.510 (Subpart H-Accelerated Approval of New Drugs for Serious and Life-Threatening Illnesses).

We remind you of your postmarketing study commitments in your submission dated October 13, 2004. These commitments are listed below.

1. Explore the feasibility of initiatives detailed below, designed to decrease the signs and symptoms of injection site reactions (ISRs).

Study NV 17658/ T20-401 “*A Phase 2 Open-label, Randomized, Active-controlled Study Comparing the Efficacy and Safety of Once Daily Enfuvirtide Dosing Versus the Currently Recommended Twice Daily Dosing in HIV-1 Infected Treatment Experienced Patients.*”

Status Report Submission: by October 31, 2005.

Final Report Submission: by December 31, 2006.

Evaluation of two formulations to allow one injection per day

Status Update Submission: by June 30, 2005.

Study T20-405 “*An Open-label, Randomized, Cross-over Study in HIV-Positive Subjects to Determine and Compare the Single-dose Pharmacokinetics of Enfuvirtide After a Single 90mg Subcutaneous Administration with the* ^{(b) (4)}-----
^{(b) (4)}----- *Needle/sy*----- -

Final Report Submission: by June 30, 2005.

Study ML18018/ Qualité “*A 12 week, Prospective, Open-label, Multicenter, Cohort Study to Assess HIV Patient Quality of Life and Tolerability After Administration of Enfuvirtide-containing HAART.*”

Protocol Submission: by December 31, 2004.

Final Report Submission: by October 31, 2006.

2. Submit a complete study report for study NV16056 (T20-310), “*Pharmacokinetic and safety study of T-20 in combination with an optimized background in HIV infected children and adolescents.*” This submission should include a comprehensive data summary and discussion of ISRs in children from all studies that included pediatric patients.

Final report submission (24 week report): by April 30, 2005

Final report submission (48 week report with ISR discussion): by August 31, 2005

A pediatric data summary on all available ISR data from studies T20-204/PACTG 1005, T20-304, and T20-305 will be included in Clinical Study Report T20-310.

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 into each study. All submissions, including supplements, relating to

these postmarketing study commitments must be prominently labeled “**Postmarketing Study Protocol**”, “**Postmarketing Study Final Report**”, or “**Postmarketing Study Correspondence.**”

While the following is not a postmarketing commitment, during our October 13, 2004 teleconference you agreed to submit a summary and analysis of interventions (from all ongoing studies and initiatives) to minimize injection site reactions (ISRs) in every annual report to IND 51,692.

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 this division 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

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

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 Virginia L. Behr, Chief, Project Management Staff, 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: approved draft labeling (package insert, patient package insert)

**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 21-481