DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21481/S-025

SUPPLEMENT APPROVAL

Hoffmann-La Roche, Inc.
c/o Genentech, Inc.
Attention: Diane deBruin, Regulatory Agent
1 DNA Way, MS #241B
South San Francisco, CA 94080-4990

Dear Ms. deBruin:

Please refer to your Supplemental New Drug Application (sNDA) dated July 16, 2012, received July 17, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Fuzeon™ (enfuvirtide) for Injection, 90 mg.

We also refer to our letter dated June 14, 2012, 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 requested in our June 14, 2012 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.

This supplemental new drug application provides for revisions to the labeling for Fuzeon™ (enfuvirtide) for Injection, 90 mg, consistent with our June 14, 2012 letter as follows (additions are noted by underline and deletions are noted by ~~strikethrough~~).

The following revisions were observed in the package insert (added text is underlined, and deleted text is ~~strikethrough~~.)

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

   ----------**RECENT MAJOR CHANGES**----------
   Warnings and Precautions (5.6) MM/YYYY

2. The date at the end of the **HIGHLIGHTS** section has been revised as follows:

   Revised: ~~08/2011~~MM/YYYY

3. 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 FUZEON. 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 jiroveci* 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.

4. The fourth bulleted paragraph of the **PATIENT COUNSELING INFORMATION** section has been revised as follows:

   FUZEON is not a cure for HIV-1 infection and patients may continue to ~~contract~~ experience illnesses associated with HIV-1 infection, including opportunistic infections. ~~The long-term effects of FUZEON are unknown at this time. FUZEON therapy has not been shown to reduce the risk of transmitting HIV-1 to others through sexual contact or blood contamination.~~ Patients should remain under the care of a physician when using FUZEON.

   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 to lower the chance of sexual contact with semen, vaginal secretions, or blood.
   - **Do not breastfeed.** We do not know if FUZEON 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.

5. The end of the package insert has been revised as follows:

   FNI_299800_PI_2012~~1~~_~~AR~~03_K

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6. **Patient Information**:

   a. The "**Does FUZEON cure HIV or AIDS?**" and the "**Does FUZEON lower the chance of passing HIV to other people?"** sections have been deleted and replaced with a **"General information about FUZEON"** section that contains the following information:

FUZEON does not cure HIV infection or AIDS. ~~People taking FUZEON may still get opportunistic infections or other conditions that can happen with HIV infection.~~ **~~For these reasons it is very important that you remain under the care of your healthcare provider while taking FUZEON~~.** 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 FUZEON.

~~FUZEON does not lower your chance of passing HIV to other people through unprotected sex, sharing needles or being exposed to your blood.~~ ~~For your own health and the health of others, it is important to continue to practice safer sex. Use a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with semen, vaginal secretions or blood. Never use dirty needles or share needles. Ask your healthcare provider if you have any questions about safer sex or how to prevent passing HIV to other people.~~

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 to lower the chance of sexual contact with semen, vaginal secretions, or blood.

b. The second bulleted paragraph in the "**Who should not use FUZEON?/Tell your healthcare provider:**" sub-section should be revised as follows:

If you are breast-feeding. ~~You should not breast-feed if you are HIV-positive because of the chance of passing the HIV virus to your baby. Also, it is not known if FUZEON can pass into your breast milk and if it can harm your baby.~~ **Do not breastfeed.** We do not know if FUZEON 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.

c. The end of the patient package insert has been revised as follows:

FNI_299800_PPI_2012~~1~~_~~AR~~03_K

Revised: ~~August 2011~~Month Year

We have completed our review of this supplemental application. It is 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 Patient Information), 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
08/10/2012