DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Andrea Czeizinger, J.D.
Program Manager
Drug Regulatory Affairs
Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, NJ 07110-1199

RE: NDA 21-481
Fuzeon™ (enfuvirtide) for Injection
MACMIS ID # 12987

Dear Ms. Czeizinger:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the Food and Drug Administration ("FDA" or the "Agency") has reviewed oral statements made by a Hoffman La-Roche, Inc. (Roche) sales representative on November 1, 2004, at the 44th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) held in Washington DC. The oral statements misbrand Fuzeon in violation of the Federal Food, Drug and Cosmetic Act (Act) and FDA implementing regulations because they recommend or suggest a use for Fuzeon that has not been approved by FDA and thus create a new "intended use" for Fuzeon for which the product lacks adequate directions. See 21 U.S.C. § 352(f)(1); 21 C.F.R. §§ 201.5(a), 201.128.

Background

According to the approved product labeling (PI), Fuzeon in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy. This indication is based on results from two controlled studies of 48 weeks duration. Subjects enrolled were treatment experienced adults; many had advanced disease. There are no studies of Fuzeon in antiretroviral naïve patients.

The Drug Resistance section of the PI states:

> HIV-1 isolates with reduced susceptibility to enfuvirtide have been selected in vitro. Genotypic analysis of the in vitro-selected resistant isolates showed mutations that resulted in amino acid substitutions at the enfuvirtide binding HR1 domain positions 36 to 38 of the HIV-1 envelope glycoprotein gp41. Phenotypic analysis of site-directed mutants in positions 36 to 38 in an HIV-1 molecular clone showed a 5-fold to 684-fold

decrease in susceptibility to enfuvirtide.

In clinical trials, HIV-1 isolates with reduced susceptibility to enfuvirtide have been recovered from subjects failing a Fuzeon containing regimen. Posttreatment HIV-1 virus from 277 subjects experiencing protocol defined virological failure at 48 weeks exhibited a median decrease in susceptibility to enfuvirtide of 33.4-fold (range 0.4-6318-fold) relative to their respective baseline virus. Of these, 249 had decreases in susceptibility to enfuvirtide of greater than 4-fold and all but 3 of those 249 exhibited genotypic changes in the codons encoding gp41 HR1 domain amino acids 36 to 45. Substitutions in this region were observed with decreasing frequency at amino acid positions 38, 43, 36, 40, 42, and 45.

Table 3 of the Clinical Studies section of the PI contains the efficacy outcomes pooled from the two pivotal clinical trials, T20-301 and T20-302. Table 3 indicates, in part:

Table 3 Outcomes at Week 48 (Pooled Studies T20-301 and T20-302)

Outcomes	**Fuzeon+Background Regimen 90 mg bid N=663**	**Background Regimen N=334**
Virological Responder (at least 1 $\log_{10}$ below baseline)	304 (46%)	61 (18%)
Virological Non-responder: - Switch - Completed 48 weeks randomized regimen*	 0 191 (29%)	 220 (66%) 12 (4%)

* Includes never responded, rebound, and missing RNA data.

At 48 weeks, 154 (23%) of subjects in the Fuzeon+background regimen and 27 (8%) in the background regimen alone had HIV RNA levels <50 copies/mL, and 225 (34%) of subjects receiving Fuzeon+background regimen had HIV RNA levels <400 copies/mL compared to 44 (13%) in the background regimen alone. Subjects achieving HIV RNA levels <50 copies/mL were included in the <400 copies/mL category and both categories were incorporated in the overall virologic responder category of achieving HIV RNA at least 1 $\log_{10}$ below baseline.

Broadening of Indication/Lack of Adequate Directions for Use

On November 1, 2004, the representative at your promotional booth at ICAAC stated, in word or in substance, that Fuzeon is appropriate for all treatment-experienced patients. By failing to disclose the limitations to the indication, i.e., that Fuzeon is appropriate only for and has been studied only in patients who are already being treated with other antiretroviral drugs who have evidence of HIV replication despite this treatment, the representative broadened the indication for Fuzeon, causing the

product's PI to lack adequate directions for the use recommended by this oral statement. Without adequate directions for such use, Fuzeon is misbranded under Section 502(f)(1) of the Act.

Similarly, the representative also claimed that Fuzeon confers "100% antiviral activity," thereby suggesting that: (1) all patients will respond to the drug, and (2) it would be appropriate for a broader range of patients than those for whom it is actually approved. As noted above, only 46% of patients in the Fuzeon-based regimen were virological responders, i.e., at least 1 $\log_{10}$ below baseline, versus 18% of patients in the background regimen. Furthermore, only 23% and 34% of patients taking Fuzeon plus background regimen, compared to 8% and 13% of patients taking background regimen alone, achieved undetectable viral load, i.e., < 50 copies/mL and < 400 copies/mL, respectively. Thus, the suggestion that all patients will respond to Fuzeon broadens the indication for the drug and causes the product's PI to lack adequate directions for the expanded use recommended by this statement.

In addition, the representative claimed that "100% of patients are susceptible to Fuzeon." At best, this statement is ambiguous. However, because its most plausible meaning is that "100% of patients respond to Fuzeon," this claim suggests that the product would be appropriate for a broader range of patients than those for whom it is actually approved, thus causing the product's PI to lack adequate directions for this expanded use. We note also that the statement is false or misleading as to Fuzeon's efficacy; the PI communicates that HIV-1 isolates with reduced susceptibility to Fuzeon have been recovered from subjects failing a Fuzeon-based regimen in clinical trials, which indicates that patients may eventually develop resistance to Fuzeon with continued therapy.

Finally, the representative claimed that Fuzeon is: "better than oral HIV drugs." Such a claim misleadingly suggests that Fuzeon is an alternative to oral HIV drugs, when in fact it is approved for use in conjunction with such drugs. Because the claim contradicts the product's PI, it causes the PI to lack adequate directions for the use recommended by this statement.

Conclusion and Requested Action

The oral statements made by your representative recommend or suggest uses for Fuzeon that have not been approved by FDA and thus misbrand Fuzeon in violation of the Act and FDA implementing regulations. See 21 U.S.C. § 352(f)(1); 21 C.F.R. §§ 201.5(a), 201.128.

DDMAC requests that Roche immediately cease the dissemination of promotional materials for Fuzeon that are the same as or similar to those described above. Please submit a written response to this letter on or before July 29, 2005, describing your intent to comply with this request, listing all promotional materials for Fuzeon that contain claims that are the same as or similar to those described above, and explaining your plan for discontinuing use of such materials. Please direct your response to Lynn Panholzer, Pharm.D., at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Room 8B-45, 5600 Fishers Lane, Rockville, MD 20857, facsimile at 301-594-6771. In all future correspondence relating to this matter, please refer to MACMIS ID # 12987 and the NDA number(s). We remind you that only written communications are considered official.

Andrea Czeizinger
Hoffman La-Roche, Inc.
NDA 21-481
MACMIS # 12987

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Fuzeon comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Lynn Panholzer, Pharm.D.
Debi Tran, Pharm.D., LT, USPHS
Regulatory Review Officers
Division of Drug Marketing,
Advertising, and Communications

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

/s/

Lynn Panholzer
7/15/05 10:38:00 AM

Debi Tran
7/15/05 10:45:22 AM