DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-087/S-045
NDA 21-246/S-031

SUPPLEMENT APPROVAL
SAFETY LABELING CHANGE NOTIFICATION

Hoffmann-La Roche Inc.
Attention: Sukirti D. Mukheja, B.S., Pharm.D.
Senior Program Manager
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Dr. Mukheja:

Please refer to your Supplemental New Drug Applications (sNDAs) dated May 13, 2008, received May 14, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for TAMIFLU (oseltamivir phosphate) capsules and oral suspension.

We acknowledge receipt of your amendments dated October 9, 2008, February 17, 2009, August 20, 2009, March 5, 2010, June 4, 2010, and November 15, 2010.

These Prior Approval supplemental new drug applications propose the following changes to the Package Insert:

1. CLINICAL PHARMACOLOGY, Microbiology
    - proposed revisions to Antiviral Activity section to include IC50 values
    - proposed revisions to Resistance section to update incidence of resistance and observed substitutions
    - proposed revisions to Cross-resistance section to include amino acid substitutions and cross-resistance between oseltamivir and zanamivir and between neuraminidase inhibitor class and M2 ion channel inhibitor class

2. DRUG INTERACTIONS
    - Proposed update on Aspirin/Tamiflu Drug-Drug Interaction

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, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at

http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert, text for the patient package insert) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. 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 via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including pending "Changes Being Effected" (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.

SAFETY LABELING CHANGE

Section 505(o)(4) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to make safety related label changes based upon new safety information that becomes available after approval of the drug or biological product.

Since TAMIFLU (oseltamivir phosphate) was approved on October 27, 1999, we have become aware of new information regarding the emergence of resistance to TAMIFLU (oseltamivir phosphate) among influenza A viruses in children. Previously, the TAMIFLU (oseltamivir phosphate) labeling stated that, in clinical trials in the treatment of naturally acquired infection with influenza virus, 1.3% (4/301) of posttreatment isolates in adult patients and adolescents, and 8.6% (9/105) in pediatric patients aged 1 to 12 years showed emergence of influenza variants with decreased neuraminidase susceptibility in cell culture to TAMIFLU (oseltamivir carboxylate). However, our resistance analyses of Trials JV16284 and WV15758 have yielded high oseltamivir resistance rates for influenza A in children and published reports have demonstrated that selection of influenza A isolates with reduced susceptibility to oseltamivir occur at high frequencies in children (Kiso et al., 2004. Lancet. 3;364(9436):759-65 and Stephenson et al., 2009. Clin Infect Dis. 48(4):389-96). We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

In accordance with section 505(o)(4) of the FDCA, we are notifying you that based on the new safety information described above and recent communications regarding NDA 21-087/S-045 and NDA 21-246/S-031 (dated December 8, 2008, July 7, 2009, July 22, 2009, November 4, 2009, March 18, 2010, September 29, 2010, and October 4, 2010), we believe that the new safety information should be included in the labeling for TAMIFLU (oseltamivir phosphate) as follows:

> Insert the following statement into the Microbiology section as the second paragraph of the Resistance subsection:

> Selection of influenza A viruses resistant to oseltamivir can occur at high frequencies in children. The incidence of oseltamivir-resistant variants in pediatric studies has been detected at rates of 27.3-36.8% and 2.9-18% for influenza A/H1N1 and influenza A/H3N2, respectively.

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a prior approval supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted. Requirements under section 505(o)(4) apply to NDAs, BLAs, and ANDAs without a currently marketed reference listed drug approved under an NDA, including discontinued products, unless approval of an application has been withdrawn in the Federal Register. Therefore, the requirements described in this letter apply to you, unless approval of your application has been withdrawn in the Federal Register.

Under section 502(z), failure to submit a response in 30 days may subject you to enforcement action, including civil money penalties under section 303(f)(4)(A) and an order to make whatever labeling changes FDA deems appropriate to address the new safety information.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

SAFETY LABELING CHANGES UNDER 505(o)(4) - PRIOR APPROVAL SUPPLEMENT

OR

SAFETY LABELING CHANGES UNDER 505(o)(4) - CHANGE NOT WARRANTED."

Prominently identify subsequent submissions related to the safety labeling changes supplement with the following wording in bold capital letters at the top of the first page of the submission:

SUPPLEMENT <<insert assigned #>>
SAFETY LABELING CHANGES UNDER 505(o)(4) - AMENDMENT

If you do not submit electronically, please send 5 copies of the submission.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

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 Elizabeth Thompson, Regulatory Project Manager, at (301) 796-0824.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, M.D.
Deputy Director of Safety
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE: 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/

ELIZABETH G THOMPSON
12/15/2010

KENDALL A MARCUS
12/15/2010