

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-246

APPROVAL LETTER



NDA 21-246

Hoffmann-La Roche Inc.
Attention: Barbara S. Taylor, Ph.D.
Program Director, Drug Regulatory Affairs
340 Kingsley Street
Nutley, NJ 07110-1199

Dear Dr. Taylor:

Please refer to your new drug application (NDA) dated June 15, 2000, received June 15, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tamiflu (oseltamivir phosphate) for Oral Suspension 12 mg/mL.

We acknowledge receipt of your submissions dated:

August 1, 2000	November 1, 2000
August 14, 2000	November 14, 2000
September 1, 2000 (2)	November 28, 2000 (2)
September 11, 2000	December 4, 2000
September 25, 2000	December 5, 2000
September 26, 2000 (2)	December 7, 2000
September 28, 2000	December 8, 2000
October 2, 2000	December 11, 2000
October 17, 2000	December 13, 2000 (4)
October 20, 2000	

This new drug application provides for the use of Tamiflu (oseltamivir phosphate) for Oral Suspension, 12 mg/mL for the treatment of uncomplicated acute illness due to influenza in patients older than one year of age who have been symptomatic for no more than two days.

We have completed the review of this application, as amended, including the updated table of drug exposures for patients with renal impairment, based on simulation in the CLINICAL PHARMACOLOGY section. We have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed package insert and submitted draft labeling (patient package insert dated December 11, 2000, and draft immediate container and carton labels dated November 14, 2000). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the FPL electronically according to the guidance for industry titled, *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 21-246." Approval of this submission by FDA is not required before the labeling is used.

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 ten of the copies on heavy-weight paper or similar material.

We remind you of your postmarketing study commitments in your submissions dated December 4, 2000 and December 13, 2000. These commitments are listed below.

1. Using all available resistant clinical isolates from both adult and pediatric trials, evaluate these isolates for cross-resistance to other neuraminidase inhibitors. Isolates should also be characterized for the emergence of drug-dependent variants.

Final Report Submission: January 2002

2. In future clinical studies (treatment or prophylaxis) further characterize the clinical aspects of infection with influenza resistant to neuraminidase inhibitors in children including: manifestations and duration of clinical disease, transmission within households or to other contacts, and virological characteristics of the isolates including detailed assessments of the kinetics of growth and clearance of resistant isolates.

Final Report Submission: January 2003

3. Complete additional studies to evaluate the antibody responses to both wild-type and resistant influenza with respect to their cross-protective potential.

Final Report Submission: January 2003

4. In additional studies, further evaluate the oseltamivir carboxylate pharmacokinetic profile (not sparse sampling) of the to-be-marketed dose of Tamiflu™ oral suspension in children younger than five years of age.

Final Report Submission: January 2003

5. Reassess the acceptance criteria for degradants in the drug product specification when the 36-month time point of the stability studies on the first three commercial scale lots of oseltamivir for oral suspension has been completed. During this reassessment, release and stability data from both commercial and representative NDA lots will be considered. These data will be submitted, with the proposed acceptance criteria, through a prior approval supplement.

Supplement Submission: January 2004

In addition, we remind you of the postmarketing commitments for the treatment and prophylaxis of

influenza virus previously agreed upon October 25, 1999 and November 17, 2000. 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."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, 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 (63 FR 66632). We note that at this time you have fulfilled the pediatric study requirement for pediatric patients one year of age and older. We are deferring the requirement for studies in neonates and infants less than one year of age until June 30, 2003.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit 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, Maryland 20857

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

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We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Grace N. Carmouze, Regulatory Project Manager, at (301) 827-2335.

Sincerely,

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

NDA 21-246 Approval letter

Concurrence:

- HFD-530/DivDir(acting)/ D. Birnkrant- 151
 - HFD-530/AssocDir/W. Dempsey- 151
 - HFD-530/MOTL/J. Murray- 151
 - HFD-530/MO/L. Lewis 151
 - HFD-530/PharmToxTL/J. Farrelly- 151
 - HFD-530/MicroTL/R. Sheets/W. Lembosev- 151
 - HFD-530/Micro/N. Battula- 151
 - HFD-530/BiopharmTL/K. Reynolds- 151
 - HFD-530/Biopharm/J. Zheng- 151
 - HFD-530/ChemTL/S. Miller- 151
 - HFD-530/Chem/D.Boring- 151
 - HFD-530/StatsTL(acting)/G. Soon- 151
 - HFD-530/Stats/A. Breazna- 151
 - HFD-530/CMS/A. DeCicco- 151
- Drafted by: GNC-December 5, 2000
- Revised: GNC
- Final: GNC
- Filename: V:\DAVDP\CSO\CARMOUZE\NDA\21246\Letters\apltr.doc
- APPROVAL (AP) (with Phase Commitments)