MAR 1 2000

NDA 21-087

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

Dear Dr. Taylor:

Reference is made to your Proposed Pediatric Study Request submitted on December 22, 1999 to IND 53,093 (serial number 190) for Tamiflu™ (oseltamivir phosphate), 75mg capsules.

To obtain needed pediatric information on oseltamivir, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies:

Type of studies:

- Adequate and well-controlled study(ies) to evaluate the safety and clinical efficacy of oseltamivir to treat children with influenza.
- Assessment of safety of oseltamivir in adolescents.
- Study(ies) to assess the pharmacokinetic profile and safety of oseltamivir in neonates and infants less than one year of age.

Indication to be studied:
Treatment of influenza virus A and B infections

Age group in which study will be performed:

- Efficacy data in children from one to twelve years of age
- Safety data in children of all ages, less than one month through adolescence
- Pharmacokinetic data in infants less than one month to one year of age

Drug information

- Dosage form:
  - 30mg per 5ml suspension and/or 60mg per 5ml suspension (neonates to twelve years of age)
  - 75mg capsule (twelve to seventeen years of age)

  There may be some overlap in age groups depending on the weight of the child and ability to swallow capsules.
- Route of administration: oral
- Regimen: to be determined

Drug specific safety concerns:

- Mild, transient nausea and vomiting, potential for development of viral resistance

Clinical Endpoints:

For efficacy studies, time to alleviation of clinical symptoms (cough and nasal symptoms) and time to return to normal activity should be the primary endpoint. Cough, nasal symptoms and activity level should be captured using a validated scale. Duration of symptoms, extent or severity of symptoms and incidence of defined secondary illnesses should be assessed. Use of concomitant medications for symptomatic relief and for secondary illnesses should also be tracked. Virologic endpoints should include proportion of study subjects with viral shedding during the follow-up period and duration of viral shedding.

Safety data should include an assessment of the potential for emergence of influenza virus resistant to oseltamivir and an attempt to characterize these strains if they are identified.

In a pharmacokinetic study, clinical endpoints are not of primary importance. Determination of pharmacokinetic parameters such as C_{max}, T_{max}, AUC, CL and half-life in young infants and appropriate dosing in this age group would be the primary analysis.

Statistical information, including power of study and statistical assessments:

Adequate numbers of children to detect clinically meaningful differences between treatment arms for confirmed influenza cases are required in the treatment efficacy studies. Analyses should include comparisons of primary endpoints between treatment groups using appropriate statistical methods including 95% confidence intervals for relative treatment effect.

Safety analyses should be included for the intent-to-treat population (those with influenza-like illness), not only the population with confirmed influenza.

An adequate number of subjects should be enrolled to determine the pharmacokinetic profile of oseltamivir in infants including neonates, taking into account what is known about inter-subject and intra-subject variability and including relevant stratification based on physiologic development.

Labeling that may result from the study:

Appropriate sections of the label may be changed to incorporate the findings of the studies.

Format of reports to be submitted:

Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation for efficacy and pharmacokinetic

studies. An analysis focusing on safety in adolescents may be submitted as a subgroup analysis from a larger study enrolling children, adolescents and adults.

Timeframe for submitting reports of the study:
Reports for the requested studies must be submitted to the Agency on or before June 30, 2003. Please remember that pediatric exclusivity extends only existing patent protection or exclusivity that has not expired or been previously extended at the time you submit your reports of studies in response to this Written Request.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as **a new drug application or as a supplement to an approved NDA** with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, call Ms. Grace Carmouze, Regulatory Project Manager, at 301/ 827-2335.

Sincerely yours,

M. Dianne Murphy, M.D. 3/1/00

M. Dianne Murphy, M.D.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Concurrence:
HFD-530/DivDir/Jolson 3/1/00
HFD-530/DepDir/Birnkrant 2/29/00
HFD-530/MOTL/Murray 2/28/00
HFD-530/MO/Wu 2/28/00
HFD-530/MO/Lewis 2/28/00
HFD-530/BiopharmTL/Reynolds 2/29/2000
HFD-530/Biopharm/Rajagopalan 2/8/00
HFD-530/CPMS/DeCicco 2.29.00
HFD-530/RPM/Carmouze 29 Feb 00

cc:
Archival NDA 21-087 and IND 53,093
HFD-530/division file
HFD-530/RPM/Carmouze
HFD-530/MOTL/Murray
HFD-530/MO/Wu
HFD-530/MO/Lewis
HFD-530/BiopharmTL/Reynolds
HFD-530/Biopharm/Rajagopalan
HFD-530/Office Director/Murphy
HFD-600/Office of Generic Drugs
HFD-2/M.Lumpkin
HFD-104/D.Murphy
HFD-002/T.Crescenzi

Drafted by: Linda L. Lewis
Initialed by: Teresa Wu
Jeffrey Murray
Final:
filename:V:\DAVDP\CSO\CARMOUZE\NDA\21-087\LETTERS\wreqletter.doc

PEDIATRIC WRITTEN REQUEST LETTER
INFORMATION REQUEST (IR)