HFD-104/Murphy

NDA 20-828

APR - 9 1999

Hoffmann-La Roche Inc.
Attn: Barbara Taylor, Ph.D.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Dear Dr. Taylor:

Reference is made to your Proposed Pediatric Study Request submitted on December 10, 1998, for FORTOVASE (saquinavir soft gelatin capsule) 200 mg to NDA 20-828.

To obtain needed pediatric information on saquinavir, 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:**

Multiple-dose pharmacokinetic, safety and activity study of saquinavir in combination with other antiretroviral agents in HIV-infected pediatric patients.

Multiple-dose pharmacokinetics and safety study of saquinavir in HIV-exposed neonates (born to HIV-infected mothers).

**Indication(s) to be studied:**

Treatment of HIV infection

**Age group in which studies will be performed:**

HIV-infected pediatric patients from one month to 16 years and HIV-exposed neonates (born to HIV-infected mothers).

**Drug information:**

Dosage form: soft gelatin capsules and age-appropriate formulation
Route of administration: oral
Regimen: to be determined by development program

**Drug specific safety concerns:**

Tolerance of capsule size, gastrointestinal adverse events, increases in hepatic transaminases, metabolic disorders such as hyperglycemia and hyperlipidemia and abnormal fat redistribution

**Statistical information:**

Descriptive analyses of multiple-dose pharmacokinetic, safety and activity data in HIV-infected pediatric patients.

Descriptive analyses of multiple-dose pharmacokinetic and safety data in HIV-exposed neonates (born to HIV-infected mothers).

Studies should include an adequate number of patients to characterize pharmacokinetics over the age range studied, taking into account inter-subject and intra-subject variability. The number of subjects should be uniformly distributed across the age range studied.

**Clinical endpoints including primary efficacy endpoints:**

Pharmacokinetics
Parameters such as $C_{max}$, $C_{min}$, $T_{max}$, $t_{1/2}$, AUC

Safety and tolerability
HIV-infected pediatric patients should be followed for safety for a minimum of six months at the recommended dose. HIV-exposed neonates (born to HIV-infected mothers) should have safety assessments, on or off treatment (as appropriate), for a minimum of six months after start of therapy. In addition, please also submit plans for long-term safety monitoring in HIV-exposed neonates and HIV-infected pediatric patients who have received FORTOVASE.

Activity
Assessment of changes in plasma HIV RNA levels and CD4 cell counts

**Labeling that may result from the studies:**

Information regarding dosing, safety and activity in HIV-infected pediatric patients and information regarding dosing and safety in HIV-exposed neonates (born to HIV-infected mothers).

**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. Please include other information as appropriate.

**Timeframe for submitting reports of the studies:**

Reports of the above studies must be submitted to the Agency on or before December 31, 2001. Please keep in mind that pediatric exclusivity only extends existing patent protection or exclusivity that has not expired at the time you submit your reports of the 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. We recommend you seek a written agreement, as described in the guidance to industry (*Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act)*, with FDA before developing pediatric protocols. 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 supplement to your approved NDA or as a new drug application, as appropriate, 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, contact Ms. Christine Kelly, RN, MS, MBA, Regulatory Health Project Manager, at 301-827-2335.

Sincerely yours,

Sandra L. Kweder, MD
Acting Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Concurrence:
HFD-530/MO Team Leader/Murray 3-23-99
HFD-5530/MO/Nguyen 3-16-99
HFD-530/SCSO/DeCicco 3-19-99
HFD-530/MO Team Leader/Cvetkovich 3-23-99
HFD-530/DD/Birnkrant 3-17-99
HFD-530/Director/Jolson 4/2/99

cc:
Archival NDA 20-828
HFD-530/division file
HFD-530PM/Kelly
HFD-530/MedicalTeam Leader/Murray
HFD-530/MO/Nguyen
HFD-600/Office of Generic Drugs
HFD-2/MLumpkin
HFD-104/DMurphy
HFD-6/KRoberts

Drafted by: cmk/December 28,1998

Address: v drive/Kelly/ind/41,099/letters/pedexclu

**PEDIATRIC WRITTEN REQUEST LETTER**
**INFORMATION REQUEST (IR)**