DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-628
NDA 20-828
NDA 21-785
IND 41,099

Hoffmann-La Roche, Inc.
Attention: Karen H. Noh, Pharm D
Senior Program Manager
Pharma Development, Regulatory
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Dr. Noh:

Reference is made to your Investigational New Drug (IND) 41,099 (saquinavir mesylate) dated January 7, 1993. Also, reference is made to your Proposed Pediatric Study Request submitted December 10, 1998. Additionally, reference is made to the Written Request for saquinavir issued April 9, 1999, as amended in the December 20, 2001 Written Request. Finally, reference is made to your request for further amendment to the Written Request as described in your submission dated April 19, 2004.

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. This Written Request supersedes all earlier versions.

Type of studies:

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

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

The objective of these studies will be to determine the pharmacokinetic and safety profile of saquinavir boosted with ritonavir or lopinavir/ritonavir across the age range studied, identify an appropriate dose of saquinavir for use in HIV-infected pediatric patients, and evaluate the activity of this dose (or doses) in treatment

Indication to be studied:

Treatment of HIV infection in combination with other antiretroviral agents in pediatric patients

Age group in which studies will be performed:

HIV-infected pediatric patients from 4 months to adolescence

Drug Information:

Dosage forms: Saquinavir mesylate 200 mg hard gelatin capsules (INVIRASE®) or saquinavir 200 mg soft gelatin capsules (FORTOVASE®) and age appropriate-formulation. The studies described above should use an age-appropriate formulation of saquinavir**.** The relative bioavailability of this formulation should be determined and compared with the marketed formulation of saquinavir. If available, full study reports of any relative bioavailability studies must be submitted to the Agency. If an age-appropriate formulation cannot be developed, complete documentation of your attempts and a detailed explanation of why the attempts were unsuccessful must be submitted. Under these circumstances other formulations can be used, if they are standardized, palatable, and shown in adults to be of acceptable relative bioavailability (compared with the marketed product).

Route of administration: oral

Regimen: to be determined by development program

Drug specific safety concerns:

Based on available toxicity information with your product, provide the following specific safety parameters that your pediatric program will address:

- Tolerance of capsule size and palatability
- Gastrointestinal adverse events
- Increases in hepatic transaminases and bilirubin
- Metabolic disorders such as hyperglycemia, hyperlipidemia, and abnormal fat redistribution

Safety of saquinavir must be studied in an adequate number of pediatric patients to characterize adverse events across the age range.

Statistical information, including power of study and statistical assessments:

Descriptive analyses of multiple-dose pharmacokinetic, safety and activity data in HIV-infected pediatric patients. A minimum number of pediatric patients (as stated below) must complete the pharmacokinetic study(ies) conducted to characterize pharmacokinetics for dose selection. Final selection of sample size for each age group should take into account all potential sources of variability. As study data are evaluated, the sample size should be increased as necessary for characterization of pharmacokinetics across the intended age range.

4 months to < 2 years: 8

2 years to < 6 years: 12

6 years to < 12 years: 8

12 years to 18 years: 6

Studies must include an adequate number of patients to characterize pharmacokinetics and select a therapeutic dose for the age ranges studied, taking into account inter-subject and intra-subject variability. The number of patients should be generally well distributed across the age range studied.

Study Endpoints:

Pharmacokinetics

Parameters such as C_{max}, C_{min}, $T_{max,}$ $t_{1/2}$, AUC and apparent oral clearance.

Safety and tolerability

HIV-infected pediatric patients must be followed for safety for a minimum of six months at the recommended dose. In addition, submit plans for long-term safety monitoring in HIV-infected pediatric patients who have received saquinavir.

Safety data must be collected on 50 to 100 pediatric patients.

Activity

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

Labeling that may result from the study(ies):

Information regarding dosing, safety and activity in HIV-infected pediatric population

Format of reports to be submitted:

Full study reports or clinical study reports containing 6-month follow-up data not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. Include other information as appropriate. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, or White. For ethnicity one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino.

Timeframe for submitting reports of the study(ies):

Reports of the above studies must be submitted to the Agency on or before March 31, 2006. Please keep in mind that pediatric exclusivity attaches only to 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.

Response to Written Request:

As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

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 your 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.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. The type of response to the Written Request (complete or partial);
2. The status of the supplement (withdrawn after the supplement has been filed or pending);
3. The action taken (i.e. approval, approvable, not approvable); or
4. The exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the Federal Register a notification of availability.

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 Marsha Holloman at 301-827-2335.

Sincerely,

{See appended electronic signature page}

Mark J. Goldberger, MD, MPH
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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

/s/

Mark Goldberger

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