HFD-104/DMurphy

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-659 and 20-680
IND 43,718

APR 16 1999

Abbott Laboratories
Attention: Rebecca Welsh
Pharmaceutical Products Division
100 Abbott Park Road
Abbott Park, Illinois 60064-3500

Dear Ms. Welsh

Reference is made to your Proposed Pediatric Study Request submitted on January 18, 1999, for ritonavir to IND 43,718.

To obtain needed pediatric information on ritonavir, 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 ritonavir in combination with other antiretroviral agents in HIV-infected pediatric patients less than two years of age.

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

Indication to be studied:

Treatment of HIV infection

Age group in which studies will be performed:

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

Drug Information

Dosage form: oral solution
Route of administration: oral
Regimen: to be determined by development program

Drug specific safety concerns:

Asthenia, nausea, diarrhea, vomiting, anorexia, abdominal pain, taste perversion, circumoral and peripheral paresthesias, liver function test abnormalities (hepatitis),

metabolic disorders such as hyperglycemia, hyperlipidemia, and abnormal fat redistribution.

Statistical information, including power of study and statistical assessments:

Descriptive analyses of multiple-dose pharmacokinetic, safety, and activity data in HIV-infected pediatric patients less than two years of age.

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 intersubject and intrasubject 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 6 months at the recommended dose. HIV-exposed neonates should have safety assessments, on or off treatment (as appropriate), for a minimum of 6 months from the start of treatment. In addition, please also submit plans for long-term safety monitoring in pediatric patients exposed to ritonavir.

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

Labeling that may result from the study (ies):

Information regarding dosing, safety and activity in HIV-infected pediatric patients less than two years of age 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 study(ies):

Reports of the above studies must be submitted to the Agency on or before July 1, 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 Sylvia Lynche, Pharm.D., Regulatory Management Officer, at 301-827-2335.

Sincerely yours,

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

Concurrence:
HFD-530/MOTL/Murray
HFD-530/MO/Struble
HFD-530/SCSO/DeCicco
HFD-530/DD/Birnkrant
HFD-530/Director/Jolson
HFD-530/MOTL/Cvetkovich

cc:
Archival IND 43,718
HFD-530division file
HFD-530/PM/Lynche
HFD-530/MO Team Leader/Murray
HFD-5530/RRO/Struble
HFD-530/Biopharm/Reynolds/Gillespie
HFD-530/Chem/Miller,L0
HFD-104/Office Director/Dr. Murphy
HFD-600/Office of Generic Drugs
HFD-2/MLumpkin
HFD-104/DMurphy
HFD-6/Kroberts

PEDIATRIC WRITTEN REQUEST LETTER
INFORMATION REQUEST (IR)