DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-569
NDA 20-680

Abbott Laboratories
Attention: Jeanne M. Fox
Pharmaceutical Products Division
100 Abbott Park Road
Abbott Park, Illinois 60064-3500

Dear Ms. Fox

Please refer to your correspondence dated August 18, 2004, requesting changes to FDA's April 16, 1999 Written Request for pediatric studies for NORVIR (ritonavir).

We reviewed your proposed changes and are amending the Written Request. For convenience, the full text of the Written Request, as amended, follows. This Written Request supercedes the Written Request dated April 16, 1999, and amended on June 18, 2001, June 21, 2001 and June 18, 2004.

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.

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.

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.

Study 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 six months at the recommended dose. 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.

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. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. 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 of submitting reports of the study (ies):

Reports of the above studies that must be submitted to the Agency on or before June 30, 2005. 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.

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. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please 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 an approved NDA** with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, 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. In addition, 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, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

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 to the pediatric population.

If you have any questions, call Vasavi Reddy, RPh., Regulatory Project Manager, at 301-827-2413

Sincerely,

{See appended electronic signature page}
Mark J. Goldberger, M.D., M.P.H
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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