DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST – AMENDMENT #6

NDA 21-226
NDA 21-251
IND 55,984

Abbott Laboratories
Attention: Raymond Votzmeyer
Associate Director, Global Pharmaceutical Regulatory Affairs
200 Abbott Park Road
RA76, AP30-1NE
Abbott Park, IL 60064-6157

Dear Mr. Votzmeyer:

Please refer to your correspondence dated February 22, 2006, requesting changes to FDA's March 31, 1999, Written Request for pediatric studies for lopinavir/ritonavir.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on March 31, 1999 and reissued on July 3, 2002, remain the same.

Drug specific safety concerns:

Gastrointestinal effects, liver function test abnormalities, metabolic disorders such as hyperglycemia, hyperlipidemia, and abnormal fat redistribution.

Safety of lopinavir/ritonavir must be studied in an adequate number of pediatric patients or neonates to characterize adverse events across the age range. Safety data for at least 24 weeks on a minimum of 100 pediatric patients receiving the to-be-marketed dose or higher is required.

Statistical information, including power of study and statistical assessments:

Descriptive analyses of multiple-dose pharmacokinetic, safety and activity data in HIV-infected pediatric patients and descriptive analyses of multiple-dose pharmacokinetic and safety data in HIV-exposed neonates (born to HIV-infected mothers). A minimum number of pediatric patients (as stated below) should 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.

Birth to < 6 weeks: 8

6 weeks to < 6 months: 6

6 months to < 2 years: 6

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. Since accurate lopinavir/ritonavir PK determinations require that the drug be given for at least 2 weeks in children in order to be at steady-state, age groups for PK will be based on subjects' age at the time of enrollment.

Format of reports to be submitted:

Full study reports or interim study reports documenting at least 24 weeks of study drug dosing 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 for submitting reports of the studies:

On or before January 31, 2008

Reports of the above studies must be submitted to the Agency on or before January 31, 2008. 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.

Reports of the studies that meet the terms of the Written Request dated March 31, 1999, as amended by this letter, must be submitted to the Agency on or before January 31, 2008, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

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.

Submit reports of the studies 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.

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 Karen Winestock, Regulatory Project Manager, at 301-796-0834.

Sincerely,

{See appended electronic signature page}

Edward M. Cox, M.D., MPH
Acting Director
Office of Antimicrobial Products
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/

Edward Cox

5/3/2007 12:25:50 PM