DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 51,979

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Charles Mazzarella
Senior Associate Director, Drug Regulatory Affairs
900 Ridgebury Rd
P.O. Box 368
Ridgefield, CT 06877-0368

Dear Mr. Mazzarella:

Reference is made to your correspondence dated August 31, 2006 requesting changes to FDA's Written Request for pediatric studies for tipranavir. We have reviewed your questions and we are amending the Written Request to:

- extend the timeframe for submitting study reports
- modify the sections "Type of studies" and "Age groups in which studies will be performed"

For clarity, the full text of the Written Request, as amended, follows.

Type of study:
Multiple-dose pharmacokinetic, safety, and activity study of tipranavir in combination with low dose ritonavir together with other antiretroviral agents in HIV-infected treatment-experienced pediatric patients.

The objective of this study will be to determine the pharmacokinetic and safety profile of tipranavir across the age range studied, identify an appropriate dose for use in HIV-infected treatment-experienced pediatric patients, and evaluate the activity of this dose (or doses) in treatment.

Indication to be studied:
Treatment of HIV-1 infection.

Age group in which study will be performed:
HIV-infected treatment-experienced pediatric patients from 2 to 18 years.

Drug Information
- Dosage form: age-appropriate formulation
- Route of administration: oral
- Regimen: to be determined by development program

Use an age-appropriate formulation in the study described above. If the study you conduct in response to this Written Request demonstrates this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing

a new dosage form for which you will seek approval for commercial marketing. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval.

Development of a commercially-marketable formulation is preferable. If you cannot develop a commercially marketable age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients acceptable to the Agency. If you conduct the requested study using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the study should be characterized, and if necessary, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

Drug specific safety concerns:
Based on available toxicity information with your product, please provide safety data including assessment of gastrointestinal symptoms, rash (including Stevens-Johnson syndrome, elevated liver transaminase levels, metabolic disturbances, intracranial and other bleeding disorders, and any other parameters pertinent to use in the pediatric population.

Safety of tipranavir should be studied in an adequate number of pediatric patients to characterize adverse events across the age range. Approximately 100 patients with at least 24 weeks safety data 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.

A minimum number of pediatric patients (as stated below) should complete the pharmacokinetic studies 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.

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 must be approximately evenly 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 should be followed for safety for a minimum of 24 weeks at the recommended dose or any higher doses studied during pediatric development. In addition, please also submit plans for long-term safety in HIV-infected pediatric patients who have received tipranavir.

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

Resistance
Collect and submit information regarding the resistance profile (genotypic and phenotypic) of clinical isolates at baseline and during treatment from pediatric patients receiving tipranavir, particularly from those who experience loss of virologic response.

Labeling that may result from the study:
Information regarding dosing, safety, and activity in HIV-infected pediatric population.

Format of reports to be submitted:
You must submit a full study report not previously submitted to the Agency addressing the issues outlined in this request with full analyses, assessment, and interpretation. In addition, the report is to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study 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:
Report of the above study must be submitted to the Agency on or before December 31, 2007. 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 of your intent 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. 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 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.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov & http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.

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, please contact Jaewon Hong, Pharm.D., Regulatory Project Manager, at (301)796-2013.

Sincerely,

{See appended electronic signature page}

Edward Cox, MD, MPH
Acting Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Linked Applications	Sponsor Name	Drug Name
IND 51979	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	PNU-140690

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

/s/

JEFFREY S MURRAY
12/17/2007

EDWARD M COX
12/18/2007