DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-972
IND 49,465

Bristol-Myers Squibb Company
Attention: Crystina Cupp, Ph.D.
Manager, Regulatory Science
5 Research Parkway
Signature 91 Bldg, 3 SIG-504
Wallingford, CT 06492

Dear Dr. Cupp:

Please refer to your correspondence dated August 25, 2004, requesting changes to FDA's September 17, 1998, Written Request for pediatric studies for Sustiva™ (efavirenz). We have reviewed your proposed changes and are amending the Written Request to:

- extend the timeframe for submitting report of the study(ies)
- modify the section 'Type of study(ies)' and eliminate the section 'Study design' to allow study designs using antiretrovirals other than nelfinavir
- make it consistent with current Written Requests in format and language (for example, delineating the expected study population)

For clarity, the full text of the Written Request, as amended, follows. This Written Request supercedes all previous versions.

Type of study(ies):

Multiple-dose pharmacokinetic, safety and activity study(ies) of efavirenz in combination with other antiretroviral agents in HIV-infected pediatric patients.

The objective of this study(ies) will be to determine the pharmacokinetic and safety profile of efavirenz across the age ranges studied, identify an appropriate dose 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-1 infection in combination with other antiretroviral agents in pediatric patients.

Age group in which study(ies) will be performed:

HIV-infected pediatric patients between the ages of 3 months and 16 years.

Drug Information

- **Dosage form:** Use an age-appropriate formulation in the study(ies) described above. The relative bioavailability of the age-appropriate formulation will need to be determined and compared with the marketed formulation of efavirenz. Full reports of any relative bioavailability studies will be submitted to the Agency. If a marketable age-appropriate formulation cannot be developed, complete documentation of your attempts and a detailed explanation of why the attempts were unsuccessful will need to be submitted. Under these circumstances the Agency will consider another formulation that is standardized, palatable, and shown 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 information on the following specific safety parameters:

- Central nervous system symptoms
- Skin rash
- Liver toxicity

Safety of efavirenz **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) will 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.

3 months 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 16 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 48 weeks at the recommended dose. In addition, submit plans for long-term safety monitoring in HIV-infected pediatric patients who have received efavirenz.

Safety data must be collected on approximately 100 pediatric patients.

Activity

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

Resistance

Collect and submit information regarding the resistance profile (genotypic and phenotypic) of clinical isolates at baseline and during treatment with efavirenz from pediatric patients who fail to respond or experience loss of virologic response.

Labeling that may result from the study(ies):

Information regarding dosing, safety and activity in HIV-infected patients between the ages of 3 months and 16 years.

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 for submitting reports of the study(ies):

Reports of the above study(ies) must be submitted to the Agency on or before January 31, 2008. Please remember that pediatric exclusivity only attaches 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.

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 **new drug application (NDA) or 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.

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 to the pediatric population.

If you have any questions, call David Araojo, Pharm.D., Regulatory Project Manager, at (301) 827-2335.

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
2/28/05 10:40:20 AM