DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20-972
NDA 21-360
IND 49, 465

REVISED WRITTEN REQUEST
AMENDMENT #6

Bristol-Myers Squibb Company
Attention: Katherine Takaki, Ph.D.
Director, Global Regulatory Strategy
5 Research Parkway
Signature 91 Building, 3 Sig-515
Wallingford, CT 06492

Dear Dr. Takaki:

Please refer to your correspondence dated November 25, 2009, requesting changes to FDA's September 17, 1998, Written Request for pediatric studies for Sustiva® (Efavirenz), 50 mg and 200 mg Capsules and 600 mg Tablets.

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 September 17, 2008, and as amended on September 17, 1999, August 8, 2001, July 2, 2003, February 28, 2005, and January 31, 2008, remain the same.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Timeframe for submitting reports of the studies:

Report of the studies that meet the terms of the Written Request dated September 17, 1998, as amended by this letter and by previous amendments dated September 17, 1999, August 8, 2001, July 2, 2003, February 28, 2005 and January 31, 2008, must be submitted to the Agency on or before December 31, 2011, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit protocols for the above studies to a supplement to the 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 (240-276-

9327) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 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.

If you have any questions, call Sherly Abraham, R.Ph., Regulatory Project Manager, at (301) 796-3198.

Sincerely,

{See appended electronic signature page}

Edward M. Cox, M.D., M.P.H.
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Attachment (Complete Copy of Written Request as amended)

To obtain needed pediatric information on SUSTIVA (efavirenz), 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 studies of efavirenz in combination with other antiretroviral agents in HIV-infected pediatric patients.

The objective of these studies 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 studies 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 studies 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

Use an age-appropriate formulation in the study(ies) described above. If the studies you conduct in response to this Written Request demonstrate 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. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients.

Development of a commercially-marketable formulation is preferable. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval.

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 that are acceptable to the Agency. If you conduct the requested studies 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 studies should be characterized, and as needed, 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, 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 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.

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 Cmax, Cmin, Tmax, t1/2, 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 studies 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 studies must be submitted to the Agency on or before December 31, 2011. 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 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 (240-276-9327) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 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.

Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

If 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval), 2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act, and 3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice in accordance with section 505A(e)(2).

Under section 505A(j) of the Act, regardless of whether the studies demonstrate that SUSTIVA (efavirenz) is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the studies.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

5. the type of response to the Written Request (i.e. complete or partial response);
6. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
7. the action taken (i.e. approval, approvable, not approvable); or
8. the exclusivity determination (i.e. granted or denied).

Finally, please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you may be required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on these requirements and the submission of this information can be found at www.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.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20972	GI-1	BRISTOL MYERS SQUIBB CO	SUSTIVA
NDA-21360	GI-1	BRISTOL MYERS SQUIBB PHARMA CO	SUSTIVA (EFAVIRENZ) 300/600MG TABLETS

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

/s/

SHERLY ABRAHAM
12/23/2009

EDWARD M COX
12/23/2009