DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-453/S-003

Bristol-Myers Squibb Company
Attention: Lamine Messaoudi, D.V.M
Manager, Global Regulatory Science
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

Dear Mr. Messaoudi:

Please refer to your supplemental new drug application dated December 9, 2003, received December 10, 2003 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zerit XR® Extended-Release, (stavudine) 37.5 mg, 50 mg, 75 mg, and 100 mg Capsules.

We acknowledge receipt of your submissions dated January 27, 2004 (2), April 1, 2004 (2), and May 14, 2004 (2).

This Labeling Supplement-Post Approval Commitment includes labeling revisions to the Description, Microbiology, Precautions and Patient Information sections of the Package Insert.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, this supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the agreed-upon labeling (text for the package insert, text for the patient package insert, and immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and unapproved.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "**FPL for approved NDA 21-453/S-003**." Approval of this submission by FDA is not required before the labeling is used.

In addition, this submission fulfills Item 5 of your Phase IV Post-Marketing Commitment to determine the *in vitro* combination activity relationships of stavudine with all approved NRTIs and determine the effect of ribavirin on anti-HIV-1 activity of stavudine *in vitro.*

Futhermore, we remind you of your other postmarketing study commitments as agreed to in your submission dated December 24, 2002. These commitments are listed below:

1. Please elucidate the complete metabolic fate of stavudine in humans. This was a Phase IV commitment for the original stavudine NDA. Final report due: **4Q 2005.**

2. Please conduct and submit the results of studies or simulations in patients with impaired renal function based on the known pharmacokinetic information of both stavudine immediate and extended release formulations, if Zerit XR® is to be used in this population. Final report due: **2Q 2003.**

3. Please continue to assess genotypes and phenotypes of pre-therapy and post-therapy HIV-1 isolates from a large number of patients failing stavudine therapy. Final report due: **4Q 2004.**

4. Please evaluate the cross-resistance of stavudine resistant HIV-1 isolates to all approved NRTIs, and the efficacy of d4T against HIV-1 isolates resistant to all approved NRTIs. Final report due: **4Q 2004.**

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Antiviral Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Donald W. Reese, Pharm.D., MBA, Regulatory Project Manager, at (301) 827-2335.

Sincerely,

{See appended electronic signature page}

Debra B. Birnkrant, M.D.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV

Enclosure: Proposed Labeling (PI and PPI) dated 5/13/2004

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

/s/

Debra Birnkrant
6/4/04 01:08:27 PM
NDA 21-453