DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-453/S-004

Bristol-Myers Squibb Company
Attention: Margo Heath-Chiozzi, M.D.
Executive Director, Global Regulatory Strategy-HIV
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

Dear Dr. Heath-Chiozzi,

Please refer to your supplemental new drug application dated May 27, 2004, received June 1, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ZERIT® (stavudine) extended release capsules.

We acknowledge receipt of your submissions dated December 16, 2004, and January 12, 2005.

This supplemental new drug application provides for revisions to the package insert, specifically to update dosing recommendations in patients with renal impairment.

We have completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the agreed-upon labeling text (package insert submitted December 16, 2004, patient package insert submitted December 16, 2004).

Please submit the 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, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-453/S-004." Approval of this submission by FDA is not required before the labeling is used.

In addition, this submission fulfills Item 2 of your postmarketing study commitments as agreed to in your submission dated December 24, 2002, "to 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® (stavudine) extended release capsules are to be used in this population. Final report due: **2Q 2003**."

Furthermore, 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.**

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 non-clinical 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**."

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
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 Destry M. Sillivan, Regulatory Project Manager, at (301) 827-2335.

Sincerely,

{See appended electronic signature page}

Jeffrey Murray, M.D.
Deputy Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV

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

/s/

Jeffrey Murray

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