



NDA 20412/S-038
NDA 20413/S-030

SUPPLEMENT APPROVAL

Bristol-Myers Squibb Research and Development
Attention: Chand Sishta, Ph.D.
Director, Mature Products
Global Regulatory Sciences
P.O. Box 4000
Princeton, NJ 08543

Dear Dr. Sishta:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received October 13, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zerit[®] (stavudine) Capsules (NDA 20412) and Oral Solution (NDA 20413).

We also refer to our letter dated September 15, 2011, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for antiretroviral products. This information pertains to the risk of the autoimmune disorder as syndromes that can occur in the setting of immune reconstitution with the use of antiretroviral products.

In addition, we refer to non-safety labeling changes in our September 15, 2011 letter for all antiretroviral products based on recent studies demonstrating decreased transmission of HIV when HIV-infected patients or their uninfected partners take antiretroviral medication.

These supplemental new drug applications provide for revisions to the labeling for Zerit[®] (stavudine) Capsules and Oral Solution, consistent with our September 15, 2011, letter as follows (additions are noted by underline and deletion are noted by ~~strikethrough~~).

1. The **RECENT MAJOR CHANGES** in the Highlights section of the labeling has been revised as follows:

Dosage and Administration, Dosage Adjustment (Peripheral Neuropathy) (2.3) – removal	12/2010
Warnings and Precautions Fat Redistribution (5.5)	12/2010
<u>Immune Reconstitution Syndrome (5.6)</u>	<u>XX/2011</u>

2. The revision date has been changed from 12/2010 to 00/0000 at the end of the **HIGHLIGHTS** section and to Month XXXX in the last page of the label.
3. The **WARNINGS AND PRECAUTIONS/Immune Reconstitution Syndrome** sub-section has been revised as follows:

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including ZERIT. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.

4. In the **USE IN SPECIFIC POPULATIONS/Nursing Mothers** sub-section, a space has been deleted between "breast feed" in the first and the third sentences of this section and read as "breastfeed".
5. The **PATIENT COUNSELING INFORMATION/General** sub-section has been revised as follows:

Patients should be ~~informed~~advised that ZERIT (~~stavudine~~) is not a cure for HIV-1 infection, and that they may continue to ~~acquire~~experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should be advised to remain under the care of a physician when using ZERIT and the importance of adherence to any antiretroviral regimen including those that contain ZERIT. ~~They should be advised that ZERIT therapy has not been shown to reduce the risk of transmission of HIV-1 to others through sexual contact or blood contamination.~~

Patients should be advised to avoid doing things that can spread HIV-1 infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** ~~We do~~It is not known if ZERIT can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in breast milk.

6. MEDICATION GUIDE

- a. The last bulleted paragraph in the section “**What should I tell my healthcare provider before taking ZERIT?**”/Before you take ZERIT, tell your healthcare provider if you:” has been revised as follows:
- ~~are breast-feeding~~**breastfeeding or plan to breast-feed**~~breastfeed. Do not breast-feed~~**breastfeed while you take ZERIT.** ~~We do~~It is not known if ZERIT can be passed into your baby in your breast milk and whether it could harm your baby. The Centers for Disease Control and Prevention (CDC) recommends that HIV-infected mothers not breast-feed to avoid the risk of passing HIV infection to your baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.
- b. The second paragraph in the section “**General information about the safe and effective use of ZERIT**” should be revised as follows:

Avoid doing things that can spread HIV-1 infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or blood.

~~ZERIT has not been shown to prevent a patient infected with HIV from passing the virus to other people. To protect others, you must continue to practice safer sex and take precautions to prevent others from coming in contact with your blood and other body fluids.~~

We have completed our review of these supplemental applications. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

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, call Kyong Hyon, Safety Regulatory Project Manager, at (301) 796-0734.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Deputy Director for Safety
Division of Antiviral Products
Office Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

KENDALL A MARCUS
11/18/2011