



NDA 020412/S-36
NDA 020413/S-28

SUPPLEMENT APPROVAL

Bristol-Myers Squibb Company
Attention: Dr. Madhu Anant, M.Sc., Ph.D., RAC
Director, Mature Brand GRS
P.O. Box 4000 Princeton, NJ 08543

Dear Dr. Anant:

Please refer to your Supplemental New Drug Applications (sNDAs) dated June 11, 2010, received June 11, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Application	Supplement	Product Name
NDA 020412	S-036	ZERIT [®] (stavudine) Capsules
NDA 020413	S-028	ZERIT [®] (stavudine) for Oral Solution

We acknowledge receipt of your amendments dated October 1, 2010, November 15, 2010 and December 3, 2010.

These “Prior Approval” supplemental new drug applications propose the following changes:

1. Conversion of the US Prescribing Information (USPI) to the physician labeling rule (PLR) format with the following revisions:
 - a. Removal of Peripheral Neuropathy in Dosage Adjustment, Subsection 2.3, which contains dose reduction recommendation in patients with stavudine-associated peripheral neuropathy.
 - b. Addition of information on lipoatrophy and lipodystrophy to the WARNINGS AND PRECAUTIONS, Section 5.
 - c. Addition of lipoatrophy, lipodystrophy, and neutropenia to Postmarketing Experience, Subsection 6.3.
 - d. Addition of Subsection 8.6, Renal Impairment.
 - e. Addition of new information on the cross-resistance profile of stavudine with other thymidine analogue medications in MICROBIOLOGY, Subsection 12.4, under Cross-resistance.
2. Proposed Risk Evaluation and Mitigation Strategy (REMS).
3. Conversion of the patient package insert to a Medication Guide.

4. Revisions to the ZERIT (stavudine) Capsules container labels and ZERIT (stavudine) Oral Solution outer carton and container labels, including adding the instruction “Detach and dispense the enclosed Medication Guide to each patient.”

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

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the package insert and Medication Guide) and include the labeling changes proposed in any pending “Changes Being Effected” (CBE) supplements and any 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 these NDAs, 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.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed.

Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).” Alternatively, you may

submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Product Correspondence – Final Printed Container Label for approved NDA 020412/S-36**” or “**Product Correspondence – Final Printed Carton and Container Labels for approved NDA 020413/S-28.**” Approval of this submission by FDA is not required before the labeling is used.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

Since ZERIT (stavudine) Capsules were approved on June 24, 1994 and ZERIT (stavudine) Oral Solution was approved on September 6, 1996, we have become aware of the association of higher rates of lipoatrophy and lipodystrophy with the use of ZERIT (stavudine) Capsules and ZERIT (stavudine) Oral Solution compared to other antiretroviral therapies based on post-marketing reports and published literature. We considered this information to be “new safety information” as defined in section 505-1(b) of the FDCA.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for ZERIT (stavudine) Capsules and ZERIT (stavudine) Oral Solution to ensure the benefits of the drug outweigh the risks of lipoatrophy and lipodystrophy.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that ZERIT (stavudine) Capsules and ZERIT (stavudine) Oral Solution pose a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients’ safe and effective use of ZERIT (stavudine) Capsules and ZERIT (stavudine) Oral Solution. FDA has determined that ZERIT (stavudine) Capsules and ZERIT (stavudine) Oral Solution are products that have serious risks (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients’ decisions to use, or continue to use ZERIT (stavudine) Capsules or ZERIT (stavudine) Oral Solution. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed ZERIT (stavudine) Capsules or ZERIT (stavudine) Oral Solution.

Your proposed REMS, submitted on December 3, 2010, and appended to this letter, is approved. The REMS consists of a Medication Guide and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include, but is not limited to, an evaluation of patients’ understanding of the serious risks of ZERIT (stavudine) Capsules and ZERIT (stavudine) Oral Solution.

Assessments of an approved REMS must include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

If you currently distribute or plan to distribute an authorized generic product under this NDA, you will also need to submit a REMS, REMS supporting document, and any required appended documents for that authorized generic, to this NDA. In other words, you must submit a complete proposed REMS that relates only to the authorized generic product. Review and approval of the REMS is required before you may market your product.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 020412 or NDA 020413 REMS ASSESSMENT

**NEW SUPPLEMENT FOR NDA 020412 or NDA 020413
PROPOSED REMS MODIFICATION
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 020412 or NDA 020413
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

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 these supplements, 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.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to these NDAs to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

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

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If you have any questions, call Amalia Himaya, Regulatory Project Manager, at 301-796-3391 or the Division's main number at 301-796-1500.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.

Director

Division of Antiviral Products

Office of Antimicrobial Products

Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling

Carton and Container Labeling

REMS

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
12/10/2010