

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-453

Administrative/Correspondence Reviews



Memorandum of Project Manager's Review: Final Printed Labeling

Date of Review: August 28, 2003

NDA Number: 21-453

Date of Submission: May 6, 2003
July 29, 2003

Applicant: Bristol-Myers Squibb

Product Name: Zerit®XR (stavudine) Extended-Release Capsules

Materials Reviewed: May 6, 2003 and July 29, 2003 Final Printed Labeling (FPL)
December 31, 2002 approval letter

Background:

This Final Printed Labeling was submitted by the applicant in response to the Division's approval of this new drug application on December 31, 2002, which provides for the use of Zerit®XR (stavudine) Extended-Release Capsules 37.5 mg, 50 mg, 75 mg, and 100 mg Capsules, a new formulation of stavudine, for the treatment of HIV-1 infection in adults as part of a combination regimen.

Summary of Review

The package insert, patient package insert, immediate container and carton labels submitted electronically on May 6, 2003 and July 29, 2003 are identical to the labeling enclosed in the approval letter dated December 31, 2002.

An acknowledge and retain letter will be issued to the applicant.

Donald W Reese, PharmD, MBA
Regulatory Project Manager
Division of Antiviral Drug Products

Attachments: July 29, 2003 Final Printed Labeling

31 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(4) Draft Labeling

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/s/

Donald Reese
10/1/03 02:53:21 PM
CSO

Tony DeCicco
10/6/03 02:52:46 PM
CSO



MEMORANDUM OF TELECONFERENCES CORRESPONDENCE

Date: May 1, 2003
Sponsor: Bristol-Myers Squibb
NDA: 21-453
Drug: Zerit XR
From: Sylvia D. Lynche, Pharm.D., Regulatory Management Officer, HFD-530
Subject: Teleconference meeting minutes

The following teleconferences were labeling negotiations:
November 15, 2002, December 11, 2002, December 18, 2002, December 20, 2002 and December 23, 2002.

Attached is the label.

If you have any questions, please call Sylvia D. Lynche, Pharm.D., Regulatory Management Officer at (301) 827-2376.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Sylvia D. Lynche, Pharm.D.
Regulatory Management Officer
Division of Antiviral Drug Products

26 Page(s) Withheld

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_____ § 552(b)(4) Draft Labeling

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/s/

Sylvia Lynche
5/1/03 01:05:36 PM
CSO

**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

Date: December 10, 2002

To: Marie-Laure Papi
Senior Regulatory Associate
Global Regulatory Science

Address: Bristol-Myers Squibb
Pharmaceutical Research Institute
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

From: Sylvia D. Lynche, Pharm.D., Regulatory Management Officer, HFD-530

Through: Ko-yu Lo, Ph.D., Chemistry Reviewer, HFD-530

Concurrence: Stephen P. Miller, Ph.D., Chemistry Team Leader, HFD-530

Subject: Labeling Comments/Recommendations for ZERIT® XR Extended Release Capsules, NDA 21-453

The following information is being conveyed to you on behalf of Dr. Lo.
Please refer to your NDA 21-453 for ZERIT® XR Extended Release Capsules submitted December 10, 2001.

With regard to the chemistry section of ZERIT® XR package insert

DESCRIPTION Section

1. We recommend the following description for the drug product. Inactive ingredients in the beads and the capsule shells are listed in alphabetic order by name as recommended in USP 25 <1091> Labeling of Inactive Ingredients.

ZERIT XR (stavudine) Capsules, containing extended-release beads, are supplied for oral administration in strengths of 37.5 mg, 50 mg, 75 mg, and 100 mg of stavudine. The beads contain stavudine and the following inactive ingredients: distilled acetylated monoglycerides, ethylcellulose aqueous dispersion, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and talc. The capsule shells contain gelatin, iron oxide colorant, silicon dioxide, sodium lauryl sulfate, and titanium dioxide. The capsules are printed with edible inks.

HOW SUPPLIED Section

2. We recommend the following revisions:

- To change bottles to high-density polyethylene bottles
- To include desiccant in the packaging configuration table or add this information somewhere under the HOW SUPPLIED Section

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Sylvia D. Lynche, Pharm.D.
Regulatory Management Officer
Division of Antiviral Drug Products

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/s/

Sylvia Lynche
12/11/02 10:59:27 AM
CSO

Chemistry labeling recommendations fax

Stephen Paul Miller
12/12/02 12:39:12 PM
CHEMIST

**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

Date: December 4, 2002

To: Cathy Ku
Global Regulatory Science - CMC

Address: Bristol-Myers Squibb
Pharmaceutical Research Institute
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

From: Sylvia D. Lynche, Pharm.D., Regulatory Management Officer, HFD-530

Through: Ko-yu Lo, Ph.D., Chemistry Reviewer, HFD-530

Concurrence: Stephen P. Miller, Ph.D., Chemistry Team Leader, HFD-530

Subject: Chemistry Comments and Requests for NDA 21-453 Zerit XR[®] Extended Release Capsules

The following information is being conveyed to you on behalf of Dr. Lo.
Please refer to your NDA 21-453 for ZERIT[®] XR Extended Release Capsules submitted December 10, 2001.

With regard to ZERIT[®] XR Extended Release Capsules

1. 3.2.P.2.4. Container Closure System (Vol.1. p.50)

You state that stavudine extended release capsules will be packaged in 30 count 95 cc HDPE bottles or in 10 count foil blister cards, and not all packages will be used in all regions. Stability data for only the bottle configuration are provided in support of the NDA. Please clarify whether the bottle configuration is the only product intended for US market, hospitals, and physician samples.

2. 3.2.P.8.3.6 Statistical Analysis of Stability Data (5/31/02 Amendment, pp. 26-31)
 - a) Potency (Table T01 and Fig. F01 & F02) – Please explain the positive regression slopes for potency. Please also provide graphic displays on the rest of the stability lots and the predicted potency values at 3 years.

b) Thymine

i)

ii)

iii)

iv)

3. 3.2.P.5.1 Control of Drug Product, Specification (Vol.1, p.147)

We recommend the following acceptance criteria for impurities for ZERIT XR Extended Release Capsules:

Impurities/Degradants

Thymine	{	}
Other individual Impurities	{	}
Total Impurities	{	}

Our recommendation was based on the submitted data (release and stability) for the bottle configuration and the acceptance criterion of { } for thymine in the current DS specification.

Our recommendation for dissolution acceptance criteria was communicated previously on 11/5/02. We would like to discuss the drug product specification with you in a later telecon.

4. Labeling

Please provide hard copies of container and carton labels for all product strengths. Please also provide electronic copies (or a reference to the location in the electronic NDA).

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Sylvia D. Lynche, Pharm.D.
Regulatory Management Officer
Division of Antiviral Drug Products

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/s/

Sylvia Lynche
12/4/02 05:46:34 PM
CSO

Acceptance Criteria for Dissolution fax NDA 21-453

Stephen Paul Miller
12/10/02 10:02:47 AM
CHEMIST

**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

Date: December 4, 2002

To: Marie-Laure Papi
Senior Regulatory Associate
Global Regulatory Science

Address: Bristol-Myers Squibb
Pharmaceutical Research Institute
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

From: Sylvia D. Lynche, Pharm.D., Regulatory Management Officer, HFD-530

Through: Jenny Zheng, Ph.D., Clinical Pharmacology Reviewer, HFD-530
Kellie Reynolds, Pharm.D., Clinical Pharmacology Team Leader, HFD-530

Subject: Clinical Pharmacology labeling recommendations for NDA 21-453.

The following comment is being conveyed to you on behalf of Dr. Zheng regarding request for information.

Labeling Recommendation:

- In "Clinical Pharmacology/Pharmacokinetics in Adults/Absorption" section, please replace [] with information for HIV-infected patients.
- In Table 1, please recheck the information for Zerit XR 100 mg QD. There were only 5 patients from the ER arm whose pharmacokinetics were evaluated on Day 14. Please do not use the results from the population PK analysis.
- In "Clinical Pharmacology/Pharmacokinetics in Adults/Effect of Food on Oral Absorption" and "Dosage and Administration/Adults" sections, please indicate the amount of yogurt or applesauce (i.e. 2 tablespoons).
- In "Clinical Pharmacology/Pharmacokinetics in Adults/Effect of Food on Oral Absorption" section, please delete " []".
- In table 2, for urinary recovery of stavudine, please indicate the period of time urine was collected.
- In table 2, for ratio of CSF to plasma concentration, please indicate the time when the value was evaluated.

- In “Clinical Pharmacology/Pharmacokinetics in Adults/metabolism” section, please delete the sentence []
 - In “Clinical Pharmacology/Special Populations/Renal Impairment” section, please delete the whole paragraph and Table 3. Reword the paragraph as:
“The effects of renal dysfunction on the pharmacokinetics of the extended-release capsule have not been investigated. Data from two studies with an immediate-release formulation of stavudine indicated that the apparent oral clearance of stavudine decreased and the terminal elimination half-life increased as creatinine clearance decreased. The applicability of the results from the immediate release formulation to the extended release formulation needs to be further investigated.” []
- J
- Please delete Tables 4 and 5. Include the information in text (one sentence), because no significant interactions were observed.
 - Please delete the last paragraph on Page 9 of the label. Complete metabolic fate of stavudine has not been evaluated.

Other Recommendation:

We sent you a recommendation for the Zerit XR dissolution specification on November 5, 2002. In addition, we also do not accept the results of the IVIVC. In order to establish IVIVC, we recommend that:

- External validation needs to be performed. Although a Level A IVIVC model based on the mean convolution approach with non-linear time scaling and in vitro dissolution data at pH 1.2 passed internal validation, other approaches all failed the internal validation.
- An IVIVC model based on individual assessment needs to be established. A mean convolution method is not acceptable.

Potential Phase IV Commitments:

1. Please elucidate the complete metabolic fate of stavudine in humans. This was a Phase IV commitment for the original stavudine NDA, and we have not received any information regarding the plan for the study.
2. Please conduct studies or simulations for renal impaired subjects based on the known pharmacokinetic information of both stavudine IR and ER, if stavudine ER is desired to be used in renal impaired subjects.

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Sylvia D. Lynche, Pharm.D.
Regulatory Management Officer
Division of Antiviral Drug Products

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/s/

Sylvia Lynche
12/4/02 03:08:12 PM
CSO

Clinical Pharmacology Labeling recommendations fax

Kellie Reynolds
12/4/02 03:34:14 PM
BIOPHARMACEUTICS

**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

Date: November 19, 2002

To: Marie-Laure Papi
Senior Regulatory Associate
Global Regulatory Science

Address: Bristol-Myers Squibb
Pharmaceutical Research Institute
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

From: Sylvia D. Lynche, Pharm.D., Regulatory Management Officer, HFD-530

Through: Lalji Mishra, Ph.D., Microbiology Reviewer, HFD-530
Jules O'Rear, Ph.D., Microbiology Team Leader, HFD-530

Subject: Microbiology Labeling comments for NDA 21-453

Listed below are modifications that have been to microbiology section of the Zerit XR label by the microbiology review team, Drs. Mishra and O'Rear. Please review and provide us with your response.

MICROBIOLOGY LABEL**Mechanism of action**

Stavudine, a nucleoside analogue of thymidine, is phosphorylated by cellular kinases to the active metabolite stavudine triphosphate. Stavudine triphosphate inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate thymidine triphosphate ($K_i = 0.0083$ to 0.032 μM) and by causing DNA chain termination following its incorporation into viral DNA. Stavudine triphosphate inhibits cellular DNA polymerases β and γ and markedly reduces the synthesis of mitochondrial DNA.

Antiviral activity

The *in vitro* antiviral activity of stavudine was measured in peripheral blood mononuclear cells, monocytic cells, and lymphoblastoid cell lines. The concentration of drug necessary to inhibit HIV-1 replication by 50% (IC_{50}) ranged from 0.009 to 4 μM against laboratory and clinical isolates of HIV-1. Stavudine had additive and synergistic activity in combination with didanosine and

zalcitabine, respectively, in vitro. Stavudine combined with zidovudine had additive or antagonistic activity in vitro depending upon the molar ratios of the agents tested. The relationship between in vitro susceptibility of HIV-1 to stavudine and the inhibition of HIV-1 replication in humans has not been established.

Drug Resistance

HIV-1 isolates with reduced susceptibility to stavudine have been selected in vitro (strain-specific) and were also obtained from patients treated with stavudine. Phenotypic analysis of HIV-1 isolates from 61 patients receiving prolonged (6-29 months) stavudine monotherapy showed that post therapy isolates from 4 patients exhibited a 7- to 16-fold decrease in susceptibility to stavudine compared to baseline isolates. Of these, HIV-1 isolates from one patient contained the zidovudine resistance-associated mutations, T215Y and K219E and isolates from another patient contained the multiple-nucleoside-resistance-associated mutation Q151M. Mutations in the RT gene of HIV-1 isolates from the other 2 patients were not detected. The genetic basis for stavudine susceptibility changes has not been identified.

Cross-resistance

Several studies have demonstrated that prolonged stavudine treatment can select and/or maintain mutations associated with zidovudine resistance. HIV-1 isolates with one or more zidovudine resistance-associated mutations (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) exhibited reduced susceptibility to stavudine in vitro 1

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Sylvia D. Lynche, Pharm.D.
Regulatory Management Officer
Division of Antiviral Drug Products

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/s/

Sylvia Lynche
11/20/02 10:50:18 AM
CSO

Microbiology Labeling fax.

Julian O Rear
11/21/02 02:00:33 PM
MICROBIOLOGIST



MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: November 5, 2002

To: Marie-Laure Papi
Senior Regulatory Associate
Global Regulatory Science

Address: Bristol-Myers Squibb
Pharmaceutical Research Institute
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

From: Sylvia D. Lynche, Pharm.D., Regulatory Management Officer, HFD-530

Through: Ko-yu Lo, Ph.D., Chemistry Reviewer, HFD-530
Jenny H. Zheng, Ph.D., Clinical Pharmacology Reviewer, HFD-530

Subject: Acceptance Criteria for Dissolution

The following requests for information are being conveyed to you on behalf of Drs. Lo and Zheng. Please refer to your NDA 21-453 for ZERIT® XR Extended Release Capsules submitted December 10, 2001.

We recommend the acceptance criteria for dissolution for ZERIT® XR Extended Release Capsules be established as follow:

2 hours [] dissolved
8 hours [] dissolved
16 hours [] dissolved

Our recommendation is based on dissolution data from the clinical/bioavailability lots in accord with FDA Guidance for Industry "Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations" for a product without an IVIVC, and dissolution data (release and stability) from the stability lots submitted in the NDA.

Page: 3
November 7, 2002

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Sylvia D. Lynche, Pharm.D.
Regulatory Management Officer
Division of Antiviral Drug Products

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/s/

Sylvia Lynche
11/7/02 11:39:03 AM
CSO

Steve I notice you had sent this fax back for revisions. The only thing I was able to see was the header had 11/6/02 instead of 11/5/02. If this not the case please send me an e-mail as to what revisions you would like made.

Stephen Paul Miller
11/25/02 03:32:53 PM
CHEMIST

As noted in revision comments, this document is an early version of the fax. The fax that was actually sent was signed by Drs. Lo, Miller, and Reynolds (as TL and for Dr. Zheng).

Kellie Reynolds
12/4/02 03:18:05 PM
BIOPHARMACEUTICS

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 24, 2002

TO: Debra Birnkrant, M.D., Director
Division of Antiviral Drug Products
HFD-530

VIA: Sylvia Lynche, Regulatory Management Officer
Division of Antiviral Drug Products
HFD-530

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Regulatory Health Project Manager
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Anne Trontell, M.D., M.P.H., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review of Patient Labeling for Zerit® XR (stavudine)
Extended-Release Capsules, NDA 21-453

The patient labeling which follows represents the revised risk communication materials for Zerit® XR (stavudine) Extended-Release Capsules, NDA 21-453. The revisions reflect changes in format, wording, and organization that are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds and have been reviewed by our office and by DDMAC. Comments are bolded, italicized, and underlined.

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✓ § 552(b)(4) Draft Labeling

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/s/

Jeanine Best
9/25/02 04:47:44 PM
CSO

Anne Trontell
9/27/02 12:18:25 PM
MEDICAL OFFICER



MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: September 18, 2002

To: Marie-Laure Papi
Senior Regulatory Associate
Global Regulatory Science

Address: Bristol-Myers Squibb
Pharmaceutical Research Institute
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

From: Sylvia D. Lynche, Pharm.D., Regulatory Management Officer, HFD-530

Through: Susan Zhou, Ph.D., Mathematical Statistician Reviewer, HFD-725
Guoxing Soon, Ph.D., Mathematical Statistician Team Leader, HFD-725

Subject: ZERIT® XR (stavudine) Statistical comments.

The following comments are being conveyed to you on behalf of Drs. Zhou and Soon.

1. For study 099 and 096, for each blood sample drawn, please clarify if you have kept a frozen sample? If yes, is the storage and frozen done according to the instructions in assay kit?
2. Please substantiate your explanation for higher ambient viral load measurement.
3. Please identify sites that continued to use samples at ambient temperature after January 1, 2001.
4. If the analyses are completed as discussed in the September 16, 2002 teleconference (using only HIV RNA measurements based on samples that adhered to the instructions), please provide these analyses when they are available.

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Sylvia D. Lynche, Pharm.D.
Regulatory Management Officer
Division of Antiviral Drug Products

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/s/

Sylvia Lynche
9/18/02 03:23:58 PM
CSO

NDA 21-453 stat comments fax

Greg Soon
9/20/02 05:24:28 PM
BIOMETRICS



MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: September 12, 2002

To: Marie-Laure Papi
Senior Regulatory Associate
Global Regulatory Science

Address: Bristol-Myers Squibb
Pharmaceutical Research Institute
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

From: Sylvia D. Lynche, Pharm.D., Regulatory Management Officer, HFD-530

Through: Kendall Marcus, MD, Medical Reviewer, HFD-530
Stanka Kukich, MD, Medical Team Leader, HFD-530

Subject: Comments regarding studies 096 and 099.

The following comments are being conveyed to you by Drs. Kukich and Marcus.

1. During the review of studies 096 and 099 for the extended release formulation of stavudine (NDA 21-453) a number of issues have arisen regarding viral load measurements obtained from ambient versus frozen samples. In study 096, where information as to whether samples were frozen or ambient was provided, there appears to be a large difference in the proportions of subjects achieving undetectable viral loads when frozen samples are compared to ambient samples. In addition, when both ambient and frozen measurements are available for a single subject at a single timepoint, there appears to be a greater than expected difference between measurements.
2. In study 099 information regarding the handling of samples is not provided in the datasets, even in subjects who have multiple measurements for a single timepoint.
3. Please provide us with a rationale for the lack of uniformity in sample handling and a data analysis for both studies that addresses this issue.

We would like to discuss these issues in a teleconference schedule for Friday September 13, 2002 at 11:00am

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Sylvia D. Lynche, Pharm.D.
Regulatory Management Officer
Division of Antiviral Drug Products

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/s/

Sylvia Lynche
9/12/02 01:42:41 PM
CSO

NDA 21-453 9-12-02 fax

Stanka Kukich
9/24/02 08:35:52 AM
MEDICAL OFFICER

Memo

To: Debra Birnkrant, M.D.
Director, Division of Anti-Viral Drug Products
HFD-530

From: Alina R. Mahmud, R.Ph.
Team Leader, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420

Through: Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420

CC: Sylvia Lynche
Project Manger
HFD-530

Date: August 22, 2002

Re: ODS Consult 02-0032-1; Zerit XR (Stavudine Extended-Release Capsules)
37.5 mg, 50 mg, 75 mg, 100 mg; NDA 21-453.

This memorandum is in response to a August 9, 2002 request from your Division for a re-review of the proprietary name, Zerit XR.

DMETS has not identified any additional proprietary or established names that have the potential for confusion with Zerit XR since we conducted our initial review on May 9, 2002 (ODS consult 02-0032) that would render the name objectionable. Therefore, we have no objections to the use of this proprietary name.

DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact Sammie Beam at 301-827-3242.

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/s/

Alina Mahmud
8/23/02 11:04:04 AM
PHARMACIST

Carol Holquist
8/23/02 11:30:36 AM
PHARMACIST

**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

Date: June 28, 2002

To: Marie-Laure Papi
Senior Regulatory Associate
Global Regulatory Science

Address: Bristol-Myers Squibb
Pharmaceutical Research Institute
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

From: Sylvia D. Lynche, Pharm.D., Regulatory Management Officer, HFD-530

Through: Kendall Marcus, M.D., Medical Reviewer, HFD-530
Susan Zhou, Ph.D., Mathematical Statistician Reviewer, HFD-530
Guoxing Soon, Ph.D., Mathematical Statistician Team Leader, HFD-530

Subject: ZERIT[®] XR (stavudine)

After reviewing the Sponsor's response to the DAVDP facsimile dated March 1, 2002 regarding the Zerit[®] XR NDA, Dr. Zhou has the following comments:

1. We have not yet received the SAS programs as requested in the facsimile. At this time we are requesting again that you submit these programs to us. Please be aware that failure to do so may result in a significant delay in the review of the Zerit[®] XR NDA.
2. In the 'VRLOAD' datasets, there are many duplicates of HIV RNA measurements per individual per visit date for both the AI455-096 and AI455-099 studies. An explanation is required as to how the final HIV RNA datasets were generated in case of multiple results per visit date. Please indicate whether the multiple results of HIV RNA measurements per visit date were obtained from the same blood sample.
3. Please provide a list of lab variables with more than one measurement per visit date, such as CD4 cell counts. Please discuss how final datasets containing one measurement per visit date were generated.

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Sylvia D. Lynche, Pharm.D.
Regulatory Management Officer
Division of Antiviral Drug Products

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/s/

Sylvia Lynche
6/28/02 11:17:07 AM
CSO

Stat fax 6/28/02

Greg Soon
7/18/02 10:16:48 AM
BIOMETRICS

5/28/02

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(ODS; HFD-400)

DATE RECEIVED: February 26, 2002

DUE DATE: May 31, 2002

ODS CONSULT #: 02-0032

TO: Debra Birnkrant, M.D.
Director, Division of Anti-Viral Drug Products
HFD-530

THROUGH: Destry M. Sullivan
Project Manager
HFD-530

PRODUCT NAME:
Zerit XR
(Stavudine Extended-Release Capsules)
37.5 mg, 50 mg, 75 mg, and 100 mg

NDA SPONSOR: Bristol Myers Squibb

NDA #: 21-453

SAFETY EVALUATOR: Hye-Joo Kim, Pharm.D.

SUMMARY: In response to a consult from the Division of Anti-Viral Drug Products (HFD-530), the Division of Medication Errors and Technical Support (DMETS) has conducted a review of the proposed proprietary name "Zerit XR" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION: DMETS has no objections to the use of the proprietary name Zerit XR. In addition, DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

DMETS decision is considered tentative. The firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Phone: (301) 827-3242
Fax: (301) 443-5161

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

**Division of Medication Errors and Technical Support
Office of Drug Safety (ODS)
HFD-400; Parklawn Building Room 15B-32
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: May 9, 2002

NDA NUMBER: 21-453

NAME OF DRUG: **Zerit XR**
(Stavudine Extended-Release Capsules)
37.5 mg, 50 mg, 75 mg, and 100 mg

NDA SPONSOR: Bristol Myers Squibb

I. INTRODUCTION

This consult was written in response to a request from the Division of Anti-Viral Drug Products (HFD-530) for assessment of the proprietary name, *Zerit XR*. The container labels and package insert labeling were reviewed for possible interventions in minimizing medication errors.

The sponsor, Bristol Myers Squibb, currently markets several Zerit products in the following strengths and dosage forms:

Zerit (Stavudine Capsules: 15 mg, 20 mg, 30 mg, and 40 mg)
Zerit (Stavudine for Oral Solution: 1 mg/mL)

PRODUCT INFORMATION

Zerit XR contains the active ingredient, stavudine. Zerit XR will be an addition to the product line of Zerit Capsules and Zerit for Oral Solution currently marketed by Bristol Myers Squibb. Zerit XR will be available as stavudine extended-release capsules. Zerit XR, in combination with other antiretroviral agents, is indicated for the treatment of HIV-1 infections. The recommended daily dose of Zerit XR is based on body weight and is administered in a once-daily schedule as follows:

For patients \geq 60 kg: 100 mg QD
For patients < 60 kg: 75 mg QD

Zerit XR will be available as 37.5 mg, 50 mg, 75 mg, and 100 mg capsules.

II. RISK ASSESSMENT

The standard DMETS proprietary name review was not conducted for this consult because the proprietary name “Zerit” has been utilized in the U.S. marketplace since June 1994. An Expert Panel discussion was conducted to address concerns with the use of the modifier “XR”. In addition, the Adverse Event Reporting System (AERS) database was searched to determine if there is any confusion with the use of the proprietary name “Zerit.”

A. EXPERT PANEL DISCUSSION

A discussion was held by DMETS to gather professional opinions on the safety of the proprietary name *Zerit XR*. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel did not object to the modifier “XR”, because “XR” has been commonly used for similar “extended-release” dosage forms marketed in the U.S. (e.g., *Tegretol XR*, *Voltaren XR*, *Dilacor XR*, *Glucophage XR*, and *Effexor XR*).
2. DDMAC did not object to the proprietary name *Zerit XR* in regard to promotional claims.

B. AERS DATABASE SEARCH

1. DMETS searched the *FDA Adverse Event Reporting System (AERS)* database for all postmarketing safety reports of medication errors associated with *Zerit*. The Meddra Preferred Term (PT), “Medication Error” and the drug names, “Zerit%,” and “stavudine%”, were used to perform the search.

A total of 34 reports from the AERS search were retrieved and reviewed. Of the 34 reports reviewed, no account involved name confusion with Zerit.

2. DMETS also searched the *FDA Adverse Event Reporting System (AERS)* database for all postmarketing safety reports of medication errors associated with “XR.” The Meddra Preferred Term (PT), “Medication Error” and the drug names, “Adderall%”, “Dilacor%”, “Effexor %”, “Glucophage%”, “Tegretol%” and “Voltaren%” were used to perform the search.

A total of 69 reports from the AERS search were retrieved and reviewed. Of the 69 reports reviewed, 7 accounts involved confusion with “XR” (See Attachment I).

C. SAFETY EVALUATOR RISK ASSESSMENT

To date, the Agency has received no medication error reports involving name confusion with Zerit. Therefore, there is no evidence at this time to conclude that the proprietary name, Zerit, has significant potential for name confusion. DMETS will continue to monitor post-marketing medication errors in association with the proprietary name, Zerit.

Zerit XR contains the same active ingredient, stavudine, as the currently marketed Zerit capsules. However, Zerit XR will be available as extended-release capsules. We recognize the need to differentiate the currently marketed Zerit capsules from this new product, Zerit XR; Zerit capsules are dosed twice daily while Zerit XR will be dosed once daily. DMETS does not object to the use of the modifier "XR" for this proposed product, since this is a common practice for similar "extended-release" dosage forms marketed in the U.S. (e.g., Tegretol XR™, Dilacor XR™, Glucophage XR™, Effexor XR™, and Adderall XR™). From the names listed above, all but Tegretol XR is dosed once daily; Tegretol XR is dosed twice daily. Based on the once a day dosing schedules, the modifier "XR" would be appropriate to identify the extended-release characteristic of Zerit XR.

According to a search in the Adverse Event Reporting System (AERS) for medication error reports with "XR", five medication error reports of confusion between Effexor and Effexor XR, one medication error report of confusion between Glucophage and Glucophage XR, and one medication error report of confusion between Adderall and Adderall XR were identified. In each case, the overlapping strength between the "non-extended release" and the "extended-release" formulations was the confounding factor that contributed to a medication error (See table 1). Overlapping strengths exist between the extended release and non-extended release formulations for Effexor XR/Effexor, Glucophage XR/Glucophage, and Adderall XR/Adderall.

Table 1

	Source AERS	Intended Product	Dispensed Product
1	3208763-8 (USP 52081)	Effexor XR 75 mg	Effexor 75 mg
2	3332283-3	Effexor 75 mg	Effexor XR 75 mg
3	3332288-2	Effexor 150 mg	Effexor XR 150 mg
4	3460522-7	Effexor XR 150 mg	Effexor 150 mg
5	3762570-6	Effexor 37.5 mg	Effexor XR 37.5 mg
6	3824270-3 (USP 54575)	Glucophage XR 500 mg	Glucophage 500 mg
7	3895548-2 (USP 54804)	Adderall XR 20 mg	Adderall 20 mg

In regards to Zerit and Zerit XR, the safety concern regarding the overlapping strength does not exist. Zerit capsules are available as 15 mg, 20 mg, 30 mg, and 40 mg while Zerit XR capsules will be available as 37.5 mg, 50 mg, 75 mg, and 100 mg. Therefore, there is insufficient evidence to render the name Zerit XR objectionable.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the draft container labels and insert labeling of Zerit XR, DMETS has focused on safety issues relating to possible medication errors. We have identified several areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABELS (37.5 mg, 50 mg, 75 mg, and 100 mg)

1. Delete the [] that appears above the proprietary name since it brings more prominence to the first four letters of the name (ZERI) and not the full name.
2. Increase the prominence of the modifier "XR" by increasing its font size so that it appears as big as the proprietary name. This will help to differentiate the labels between Zerit and Zerit XR.
3. Increase the prominence of the dosage form "Extended-Release Capsules" by increasing its font size so that it appears as big as the established name, Stavudine. Currently, the font size is too small to read.
4. The strength is not prominent and difficult to locate. Increase the font size of the strength and relocate the strength away from the quantity. In addition, relocate the strength so that it appears immediately after the established name or in conjunction with the proprietary name.

B. PACKAGE INSERT

DOSAGE AND ADMINISTRATION and Patient Information leaflet

The statement 'L] is confusing because the beads will be crushed once chewed. Please clarify this statement.

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IV. RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name Zerit XR.
2. DMETS recommends the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

DMETS decision is considered tentative. The firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam, project manager, at 301-827-3242.

Hye-Joo Kim, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety (ODS)

Concur:

Alina R. Mahmud, RPh.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Attachment I

	Source AERS	Date of Event/ Report	Intended Product	Dispensed Product	Outcome/Description
1	3208763-8 (USP 52081)	2/10/99	Effexor XR 75 mg	Effexor 75 mg	Actual Error. A prescription for Effexor XR 75 mg was dispensed with Effexor 75 mg. The patient discovered the error prior to ingestion.
2	3332283-3	3/99	Effexor 75 mg	Effexor XR 75 mg	Actual Error. A patient received Effexor XR 75 mg instead of Effexor 75 mg. She experienced dizziness, diarrhea, and fell down without any muscle coordination.
3	3332288-2	5/4/99	Effexor 150 mg	Effexor XR 150 mg	Actual Error. A patient received Effexor XR 150 mg instead of Effexor 150 mg. She took Effexor XR 600 mg daily for an unknown amount of time.
4	3460522-7	4/13/99	Effexor XR 150 mg	Effexor 150 mg	Actual Error. A patient received Effexor 150 mg instead of Effexor XR 150 mg. Within a week of taking Effexor 300 mg daily, she experienced increased blood pressure.
5	3762570-6	6/11/01	Effexor 37.5 mg	Effexor XR 37.5 mg	Actual Error. A physician dispensed samples of Effexor XR 37.5 mg instead of Effexor 37.5 mg. The error was discovered prior to ingestion
6	3824270-3 (USP 54575)	10/25/01	Glucophage XR 500 mg	Glucophage 500 mg	Actual Error. A refill for Glucophage XR 500 mg was filled with Glucophage 500 mg. A patient discovered the error prior to ingestion.
7	3895548-2 (USP 54804)	3/12/02	Adderall XR 20 mg	Adderall 20 mg	Actual Error. A prescription for Adderall XR 20 mg was dispensed with Adderall 20 mg. The pharmacist did not realize that an extended release form of Adderall was available. The patient experienced no adverse outcome.

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/s/

Hye-Joo Kim
5/28/02 11:41:52 AM
PHARMACIST

Alina Mahmud
5/28/02 11:57:25 AM
PHARMACIST

Jerry Phillips
5/28/02 12:09:49 PM
DIRECTOR

**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

Date: March 1, 2002

To: Marie-Laure Papi
Associate, Regulatory Affairs

Address: Bristol-Myers Squibb
Pharmaceutical Research Institute
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

From: Destry M. Sullivan, M.S., Regulatory Project Manager, HFD-530

Through: Joe Toerner, M.D., Medical Officer/Acting Medical Team Leader, HFD-530
Susan Zhou, Ph.D., Statistics Reviewer, HFD-530
Guoxing Soon, Ph.D., Statistics Team Leader, HFD-530

Subject: NDA 21-453, ZERIT XR

The following comments are forwarded on behalf of Dr Susan Zhou:

Due to a recent modification of the definition of virologic failure by the Division of Antiviral Drug Products (DAVDP), we request that the following efficacy analyses be performed for HIV RNA level LOQ=400 c/mL and then LOQ=50 c/mL using the attached new Time to Loss-of-Virologic Response (TLOVR) algorithm (see A2.) for Study AI455-096 and Study AI455-099, respectively. The details of the requested efficacy analyses are listed below.

1. Calculate TLOVR using the attached TLOVR algorithm and plot the corresponding Kaplan-Meier survival curves through Week 48 and beyond by treatment arms.
2. Calculate the response rates using the attached definitions for each visit through Week 48 for each treatment arm (see A1).
3. Plot the response rates over time for treatment arms.
4. Provide time and reasons for study discontinuation, adding new medications and loss to follow-up. If there are multiple reasons then they should all be accounted for. In addition, please describe the adverse events at the time of study discontinuation, adding new medications and loss to follow-up. Please explain the associations between the adverse events and deaths.
5. Classify Week 48 failures according to the primary reason for the earliest failure where the time should be determined by the TLOVR.

- A Subjects who did not complete 48 weeks of therapy and never achieved confirmed virologic suppression by the TLOVR should be classified according to reasons they failed, not simply as "Never suppressed."

Only those subjects who had completed 48 weeks of therapy but had never achieved viral load <LOQ, and had not become a virologic failure by Week 48 should be classified as "Never Suppressed" (See A3. Table 1).

- B For subjects who failed for multiple reasons at the earliest time for failure, the order for classifications is death, virologic failure, AE, and then other reasons

For example, if virologic rebound and AE resulting in discontinuation occurred at the same visit, then the patient would be classified as a virologic failure. However, if a patient discontinued due to an AE and subsequently died, then the reason for failure would be death, if the death were reasonably attributed to that AE.

6. Display the information in Step 5 in a table formatted as in A3. Table 1 below. Also, provide p-values for testing the difference in proportion of subjects with < LOQ between the two treatment arms.
7. Report all new CDC Class C events by treatment arms, including those that did not lead to study discontinuation. Note that Table 1 in A3 contains only those new CDC Class C events that led to study discontinuation and/or addition of new antiviral drugs.

Please submit SAS programs, data sets if not previously submitted, and SAS outputs. Graphs and tables should be presented in an appropriate format that can be modified by the reviewers.

If you have any questions regarding this request, please contact us as soon as possible.

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Appendix

A1. Definitions for a Non-responder (failure)

For each visit, a subject with the following events prior to or at this visit will be considered as a non-responder or failure for that visit (see details in attached A2. TLOVR algorithm) if any of the following occur:

- a) Never treated
- b) Death
- c) Permanent discontinuation of the study
- d) Introducing a new drug to the regimen
- e) Loss to follow-up
- f) Have not achieved confirmed <LOQ status or achieved confirmed <LOQ status but rebounded (i.e., two consecutive \geq LOQ copies/mL or one \geq LOQ copies/mL for the last available visit).

From the above definitions for a non-responder or failure, a subject who is not a non-responder or failure will be regarded as a responder. In other words, responders are those who had achieved viral load <LOQ that is confirmed later, prior to, or at the visit of interest, but had not yet lost the virologic response defined by the TLOVR algorithm below.

A2. Loss-of-Virologic-Response (TLOVR) Algorithm

For NDAs with 48 week virologic data, one analysis that computes time to virologic failure should follow the algorithm below.

- 1) For 2) and 3) below, discard all visits with no data. In what follows, a visit means a visit with an observed viral load. Viral load data from Time to all available visits, including off-schedule visits and post Week 48 visits, should be included for the calculation.
- 2) If a subject had never achieved confirmed HIV RNA levels below the assay limit (on two consecutive visits) before the following events, then this subject will be considered to have failed at time 0:
 - a) Death
 - b) Permanent discontinuation of the study
 - c) Loss to follow-up
 - d) Introduction of a new anti-retroviral drug to the regimen
Exceptions may be proposed for certain background drug changes where the reason for the change is due to either toxicity or intolerance that can be clearly attributed to the background drug, not the study drug or its control.
 - e) Last available visit.
- 3) For all subjects who had confirmed HIV RNA levels below an assay limit, i.e., on two consecutive visits below assay limit, the time of failure is the earliest time when a specific event had occurred. Those events are modifications in 4) and are listed below:
 - a) Death
 - b) Permanent discontinuation of the study
 - c) The event as described in 2d
 - d) Confirmed HIV RNA levels above or equal to an assay limit
Defined as HIV RNA levels from two consecutive visits are greater than or equal to an

assay limit or one visit greater than or equal to an assay limit followed by loss to follow-up

- e) Loss to follow-up.
- 4) If the time of virologic failure defined above is immediately preceded by a single missing scheduled visit or multiple consecutive missing scheduled visits, then the time of virologic failure is replaced by the first time of such missing visits.

For open-label studies, algorithms that incorporate other ways of handling missing data or treatment changes may be used for additional sensitivity analyses..

For example, sponsors should perform analyses that explore the sensitivity of the results to potential biases related to an open-label design. It is common that the no protocol-specified treatment changes are treated as failures in the study arm, and as censored at the time of change in the control arm.

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A3. Table 1. Summary of Study Outcomes

Table 1. Summary of Study Outcomes

Outcome	d4T ER+3TC+Efavirenz (N=)		d4T IR+3TC+Efavirenz (N=)	
	n	%	n	%
Responder ¹				
Virologic failure ²				
Rebound				
Never suppressed through Week 48				
Discontinued or changed therapy due to virologic failure ³				
Reasons for Discontinuation or Changed Therapy				
New CDC Class C events				
Death				
Adverse Events				
Other reasons ⁴				
Consent withdrawn				
Loss to follow-up				
Non-compliance				
Pregnancy				
Protocol violation				
Never treated				
Other				
<p>1 P-value= ...</p> <p>2 Includes</p> <p>3 Virologic failures according to case report forms.</p> <p>4 Includes ...</p>				

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Destry M. Sullivan, MS
Regulatory Project Manager
Division of Antiviral Drug Products

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/s/

Destry Sillivan
4/2/02 02:18:20 PM
CSO

Dr. Laessig, could you sign off on this, as
Joe did not, and is no longer here?

Kathrine Laessig
4/2/02 02:32:08 PM
MEDICAL OFFICER



NDA 21-453

3-1-02

Bristol-Myers Squibb Company
Attention: Marie-Laure Papi
Senior Regulatory Associate, Regulatory Science
5 Research Parkway
Wallingford, CT 06492

Dear Ms. Papi,

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: ZERIT® XR (stavudine) Capsules

Review Priority Classification: Standard (S)

Date of Application: December 10, 2001

Date of Receipt: December 10, 2001

Our Reference Number: NDA 21-453

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 8, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be October 10, 2002 and the secondary user fee goal date will be December 10, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You

should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Division Document Room 115
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, please call Destry M. Sullivan, M.S., Regulatory Project Manager, at (301) 827-2335.

Sincerely,

{See appended electronic signature page}

Anthony W. DeCicco, R.Ph.
Chief, Project Management Staff
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**

/s/

Tony DeCicco
3/1/02 04:14:45 PM



MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: February 7, 2002

To: Marie-Laure Papi
Associate, Regulatory Affairs

Address: Bristol-Myers Squibb
Pharmaceutical Research Institute
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

From: Destry M. Sullivan, M.S., Regulatory Project Manager, HFD-530

Through: Joe Toerner, M.D., Medical Officer/Acting Medical Team Leader, HFD-530
Susan Zhou, Ph.D., Statistics Reviewer, HFD-530
Guoxing Soon, Ph.D., Statistics Team Leader, HFD-530
Lalji Mishra, Ph.D., Microbiology Reviewer, HFD-530
Jules O'Rear, Ph.D., Acting Microbiology Team Leader, HFD-530
Jenny Zheng, Ph.D., Clinical Pharmacology Reviewer, HFD-530
Kellie Reynolds, PharmD., Clinical Pharmacology Team Leader, HFD-530

Subject: NDA 21-453, ZERIT XR

The following comments are forwarded on behalf of the ZERIT XR review team:

Clinical:

1. The submission of the 48-week safety and efficacy data from study AI454-099 will be anticipated during the standard review timeline. In order to conduct an adequate review, this additional data should be submitted to the NDA by June 1, 2002. The submission of the 48-week data after June 1, 2002 may be considered by DAVDP to be a major amendment to the NDA that would allow for additional time to conduct an adequate review.
2. The availability of a once-daily formulation of stavudine will be of great interest in the pediatric patient population. Please provide your plans to conduct a pharmacokinetic study in the appropriate pediatric age groups, where a deferral of the requirements for the conduct of pediatric studies will be considered. A waiver of the requirements to conduct pediatric studies in the youngest age groups that cannot tolerate a fixed-dose capsule will be considered.

Clinical Pharmacology:

3. Please provide all the individual capsule dissolution data.

4. Please provide all pharmacokinetic (PK) study reports, PK raw data, and individual patient PK parameters in electronic format.

Microbiology:

5. Please provide data on the genotypic and phenotypic analyses of HIV-1 isolates from patients who demonstrated virologic failure while receiving stavudine containing regimens in studies AI454-096 and AI454-099.

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Destry M. Sullivan, MS
Regulatory Project Manager
Division of Antiviral Drug Products

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this page is the manifestation of the electronic signature.**

/s/

Destry Sullivan
2/14/02 09:22:23 AM
CSO

Dr. Toerner, this is the facsimile for NDA 21-453,
filing meeting comments

Joe Toerner
2/15/02 09:42:21 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO (Division/Office) Sammie Beam OPSS/DMETS, HFD-400			FROM: Destry M. Sullivan, RPM, HFD-530	
DATE February 15, 2002	IND NO. 32486	NDA NO. 21-453	TYPE OF DOCUMENT General Correspondence	DATE OF DOCUMENT November 1, 2001
NAME OF DRUG Stavudine		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Antiviral	DESIRED COMPLETION DATE April 30, 2002
NAME OF FIRM Bristol Myers Squibb				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> PAPER NDA <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> MANUFACTURING <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> XOTHER (SPECIFY BELOW) <input type="checkbox"/> CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER	
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST	
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS	
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTIONS: TRADE NAME REVIEW BMS has submitted the name "Zerit XR" as the trade name for their extended-release formulation of Zerit®. As a back up to Zerit XR, they submit the name [] Please evaluate BMS' choice of names for their NDA (NDA 21-453). The PDUFA date (standard review) is October 10, 2002.				
CC:				
SIGNATURE OF REQUESTER Destry Sullivan			METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

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

/s/

Destry Sullivan
2/15/02 01:04:07 PM