CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-453

Chemistry Review(s)

NDA 21-453

ZERIT® XR
(stavudine)
Extended Release Capsules

Bristol-Myers Squibb Company

Ko-Yu Lo, Ph.D.
Division of Antiviral Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA # 21-453

2. REVIEW #: 1

3. REVIEW DATE: 12/21/2002

4. REVIEWER: Ko-Yu Lo, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	10/DEC/2001
Amendment BC	31/MAY/2002
Amendment BC	02/OCT/2002
Amendment BC	25/NOV/2002
Amendment BC	12/DEC/2002
Amendment BC	16/DEC/2002
Amendment BC	20/DEC/2002
Amendment BC	23/DEC/2002

7. NAME & ADDRESS OF APPLICANT:

Name: Bristol –Myers Squibb Company

Address: 5, Research Parkway
Wallingford, CT 06492

Representative: Marie-Laure Papi

Telephone: 203-677-6259

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ZERIT® XR
b) Non-Proprietary Name (USAN): Stavudine
c) Code Name/# (ONDC only): BMY-27857 (d4T)
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Antiviral

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 37.5 mg, 50 mg, 75 mg, and 100 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

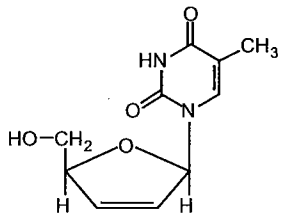
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:
_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
2',3' - didehydro -3'- deoxythymidine
CAS Reg. No.

Synonym:	d4T
Molecular Formula	$C_{10}H_{12}N_2O_4$
Molecular Weight	224.2

Structure Formula



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	III	[redacted]	[redacted]	4	N/A		Container of identical composition but in different size has been found adequate
[redacted]	III	[redacted]	[redacted]	3	Adequate	5/12/99	
[redacted]	III	[redacted]	[redacted]	4	N/A		Container of identical composition for has been found adequate
[redacted]	III	[redacted]	[redacted]	3	Adequate	4/25/02	
[redacted]	III	[redacted]	[redacted]	3	Adequate	9/10/97	
[redacted]	IV	[redacted]	[redacted]	3	Adequate	7/31/02, 8/13/02	See Review for additional information on BSE issue

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA Chemistry Reviews	NDA 20-412 Original	CMC for stavudine drug substance
Supplement Chemistry Review	NDA 20-412/S014	[redacted] ' Process for stavudine drug substance
IND	32,486	Stavudine Extended Release Capsules

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	10/7/02	HFD-322
Pharm/Tox	N/A		
Biopharm	Dissolution Specification Acceptable	12/20/02	Jenny Zheng & Ko-Yu Lo
LNC	N/A		
Methods Validation	Pending		
OPDRA	Acceptable	9/24/02	
EA	Exclusion Acceptable		Ko-Yu Lo
Microbiology	N/A		

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-453

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a chemistry, manufacturing, and controls standpoint, the NDA is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance, stavudine, is a synthetic thymidine nucleoside analogue active against the human immunodeficiency virus (HIV). The CMC information for the stavudine drug substance is crossed referenced to the approved NDA 20-412 original and supplement S014. Pertinent information is summarized for reference purpose:

Stavudine is a white to off-white crystalline powder with an aqueous solubility of 83.4 mg/mL at 23°C. The drug substance is stable when stored at temperatures up to 30°C, but degrades to thymine [ ] under extreme stress conditions (50°C or 37°C/87%RH for [ ]. Depending on the conditions [ ]

] The solubility profiles of all [ ] are similar. Bulk drug substance manufactured by the two approved processes [ ] is [

]

the stress conditions tested [ ] Based on these data, bioavailability issues [ ] are not anticipated. Stavudine is currently available as ZERIT® Capsules (an immediately release dosage form) in the strengths of 15, 20, 30 and 40 mg, and as ZERIT® for Oral Solution (1mg/mL upon reconstitution).

The drug product, ZERIT® XR Extended Release Capsules is an extended-release bead formulation encapsulated in hard gelatin shells in strengths of 37.5, 50, 75 and 100 mg. All strengths utilize the same coated beads and differ only in the fill weight required to

obtain label potency. ZERIT® XR Extended Release Capsules are manufactured via a process [redacted]

[redacted] Critical parameters and in-process controls have been identified and established. Specification for the drug product includes description, identification (IR and HPLC), assay (HPLC), impurities (degradants by HPLC), content uniformity, dissolution, and microbial limits. Stability data were generated on [redacted] commercial-scale lots [redacted] for up to [redacted] at 25°C/60%RH and 30°C/60%RH, and for [redacted] at 40°C/75%RH. The assay ranged from [redacted] at [redacted] @ 25°C/60%RH and the common slop regression model shows a LCL slope of [redacted] per year. The major degradant, thymine (as well as total impurities) ranged from [redacted] at [redacted] months @ 25°C/60%RH with a predicted value of [redacted] at [redacted] (UCL of regression curve). Acceptance criteria for thymine and total impurities are established based on release and stability data using linear regression analysis and 95% confidence interval approach for a potential shelf-life of [redacted] Acceptance criteria for dissolution are established based on data from the clinical lots and data (release and stability) from the stability lots.

B. Description of How the Drug Product is Intended to be Used

ZERIT® XR, in combination with other antiretroviral agents, is indicated for the treatment of HIV-1 infection. The recommended dose is 100 mg once daily for patients ≥60 kg and 75 mg once daily for patients <60 kg. ZERIT® XR Capsules are packaged into high-density polyethylene (HDPE) bottles as 30 counts per bottle with 1.5 g of desiccant (silica gel). The bottles are stored at 25°C (77°F), excursions permitted to 15-30°C (59-86°F).

A twenty-four months expiration dating period is approved based on [redacted] long term stability data at both 25°C/60% RH and 30°C/60% RH for [redacted] commercial-scale batches using linear regression analysis and 95% confidence interval approach.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments ultimately provided adequate information on the chemistry, manufacturing and controls for the production of ZERIT® XR Extended Release Capsules, 37.5 mg, 50 mg, 75 mg and 100 mg.

The potency/assay of the drug product is well within the established acceptance criteria [redacted] in [redacted] although the linear regression indicates a positive trend. Per FDA request, reanalysis of thymine data using regression analysis as well as a worse case scenario to predict the thymine levels at [redacted] were conducted. Based on this data the regulatory acceptance criteria for thymine and total impurities were established. The acceptance criteria for dissolution were discussed

extensively in a teleconference, and agreed-upon subsequently. As amended all methods and acceptance criteria were found acceptable for the drug product.

After pre-approval inspection, all manufacturing and testing facilities were found acceptable.

Higher than normal dissolution for coated beads was noticed during the process of validation. The applicant's investigation plan was discussed during 11/15/02 and 12/20/02 teleconferences. Time line for new studies and completion of validation is targeted for 1/2Q 2003. BMS commits not to launch the product prior to the completion of validation process.

III. Administrative

A. Reviewer's Signature

Chemist:
Ko-Yu Lo, Ph.D. *{Signed Electronically in DFS}*

B. Endorsement Block

ChemistryTeamLeader
Stephen P. Miller, Ph.D. *{Signed Electronically in DFS}*

C. CC Block

HFD-830 Division Director
Chi-wan Chen, Ph.D.