CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-294

CHEMISTRY REVIEW(S)

NDA 22-294

Zidovudine Tablets USP 60 mg
(Pediatric Strength)

Aurobindo Pharma Limited
INDIA

Division of Anti-Viral Drug Products
HFD-530
CDER – FDA

Ted Chang, Ph.D.
ONDQA Pre-Marketing Assessment and
Manufacturing Science Division III–Branch VI

Table of Contents

CMC Review Data Sheet

1. NDA 22-294

2. REVIEW #: 1

3. REVIEW DATE: June 5, 2009

4. REVIEWER: H. Ted Chang, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	Subject Title
Pre-submission (M)	18-DEC-2007	
Pre-submission (M-BC)	11-MAR-2008	Stability Data
Pre-submission (M-BL)	17-MAR-2008	Labeling
Pre-submission (RRC)	25-JUN-2008	Stability Data
Amendment (RRZ)	22-AUG-2008	Stability Data (split tablet) and Labeling
Amendment (RRC)	4-SEP-2008	Residual Solvents USP <467>
Original (N)	03-OCT-2008	Zidovudine Tablets USP 60 mg
Amendment (N-BL)	03-APR-2009	Labeling

7. NAME & ADDRESS OF APPLICANT:

Name	Aurobindo Pharma Limited
Address	Plot No.2, Maitrivihar, Ameerpet Hyderabad – 500 038 Andhra Pradesh INDIA
Representative	Mr. Madan Mohan Reddy
Telephone	91-40-23044074
Drug Establishment No.	3004021229

U.S. Agent:

CMC REVIEW

CMC Review Data Sheet

Name	Aurobindo Pharma Limited
Address	2400 Route 130 North, Dayton, NJ 08810 U.S.A.
Representative	Mr. Prasada Kambham
Telephone	1-732-839-9406

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name	N/A
Non-Proprietary Name (USAN)	Zidovudine Tablets USP
Code Names	ZD, ZDE, AZT, ZDV
Chemistry Type	4
Submission Priority	P*

* The review priority was changed to Standard (from Priority) because the patent has expired and a full approval is considered.

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2) under PEPFAR (Reference drug: RETROVIR® Zidovudine Tablets 300-mg, GlaxoSmithKline)

10. PHARMACOL. CATEGORY: Used in combination with other antiretroviral agents is indicated for the treatment of HIV infection.

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 60 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__ Rx _____OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

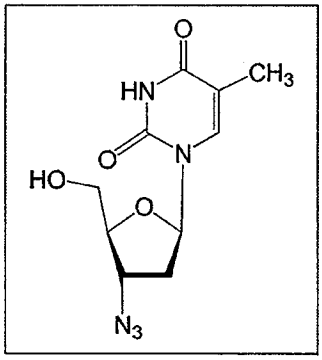
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Names: Thymidine, 3'-azido-3'-deoxy-

CMC Review Data Sheet

or, 3'-azido-3'-deoxythymidine

US Adopted Name (USAN): Zidovudine USP
International Non-proprietary Name (INN): Zidovudine
Laboratory Codes: ZD, ZDE



Chemical Formula: $C_{10}H_{13}N_5O_4$
Molecular Weight: 267.24
CAS Number: 30516-87-1

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
18714	II	Aurobindo Pharma	Zidovudine USP	3	Adequate	08-JUL-2008	Reviewed by G. Lunn, ONDQA
[redacted]	IV	[redacted]	[redacted]	4			
[redacted]	IV	[redacted]	[redacted]	4			
[redacted]	IV	[redacted]	[redacted]	4			
[redacted]	IV	[redacted]	[redacted]	4			
[redacted]	III	[redacted]	[redacted]	4			
[redacted]	III	[redacted]	[redacted]	4			

b(4)

CMC Review Data Sheet

[redacted]	III	[redacted]	[redacted]	4			
[redacted]	III	[redacted]	[redacted]	4			
[redacted]	III	[redacted]	[redacted]	4			
[redacted]	III	[redacted]	[redacted]	4			
[redacted]	III	[redacted]	[redacted]	4			
[redacted]	III	[redacted]	[redacted]	4			
[redacted]	III	[redacted]	[redacted]	4			
[redacted]	III	[redacted]	[redacted]	4			

b(4)

[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)

Letters of Authorization for DMFs are provided in the M1 Admin.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A	N/A	N/A

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable–OC	07-MAR-2008	S. Adams
LNC	N/A		
Methods Validation	Not required		
OSE DMETS	N/A		
EA	Categorical Exclusion: Acceptable	23-SEP-2008	T. Chang
Microbiology	Not required		

CMC Review for NDA 22-294

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for approval from the CMC perspective. All CMC issues have been reviewed and found satisfactory and an overall recommendation of Acceptable has been made by the Office of Compliance.

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

None

II. Summary of CMC Assessments

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

The drug product is manufactured using drug substance zidovudine manufactured by Aurobindo Pharma Ltd. under DMF 18714. Letters of Authorization to refer to the DMF is provided. The DMFs have been reviewed and found to be adequate.

Some drug substance information is incorporated in this NDA. However, the acceptability of the drug substances is based on review of the DMF. The drug substance is manufactured by Aurobindo in a facility in Andhra Pradesh, India. An Overall Recommendation of Acceptable has been made in EES.

Satisfactory drug substance specifications are supplied. The specifications are in accord with those in the USP. Tests for melting range, particle size, microbial limits, and density are added. The residual solvent specifications are set to match the requirements of the manufacturing process. All limits conform to ICH Q3C. The analytical methods are described at a satisfactory level of detail.

The tablets contain 60 mg zidovudine and the inactive ingredients are microcrystalline cellulose, sodium starch glycolate, hypromellose, magnesium stearate, [redacted] [redacted] film coat, and purified water. The magnesium stearate is of vegetable origin. The components [redacted] are hypromellose 6 cp, titanium dioxide, and PEG 400. All inactive ingredients are compendial or are made of compendial materials. This product is a scaled-down formulation of the zidovudine 300 mg tablet that was

b(4)

approved in ANDA 77-267 and so extensive pharmaceutical development work has not been carried out.

The drug product will be manufactured by Aurobindo Pharma Limited in Andhra Pradesh, India. An Establishment Evaluation Request was submitted and an Overall Recommendation of Acceptable has been made. The manufacturing process is described at a reasonable level of detail.

Reasonable drug product specifications for appearance, identity, average weight, water dissolution, uniformity, impurities, and assay are provided. The analytical methods are the same as approved ANDA 77-267 and are described at a reasonable level of detail. No novel impurities are identified. A justification of the specifications is provided. The tablet does not have a residual solvent specification but the sponsor has committed to complying with USP <467> and to submitting the supporting data within 6 months of approval.

Satisfactory analytical data are provided for 3 batches of ——— tablets manufactured in July 2007. Tablets described in this application were made from the same blend as higher strength tablets which were shown to be bioequivalent to a Reference Listed Drug (Zidovudine tablets 300-mg). b(4)

The container-closure systems are 40 cc ——— bottles containing 60 tablets (with Child-Resistant closures and induction seals), 120 cc bottles containing 1000 tablets (with screw-cap closures and induction seals), ——— /aluminum foil blister packs of 10, ——— ——— The components are covered by DMFs. Satisfactory container labels are supplied. b(4)

Satisfactory stability data are reported for 3 batches stored at 30°C/75% RH and 40°C/75% RH for 6 months in each packaging configuration. In addition satisfactory data are provided for one batch stored at 25°C/80% RH and 50°C for 3 months. There are no out of specification results and no pronounced trends. The proposed expiration dating period of 24 months is acceptable. The first 3 commercial batches in the blister pack and the smallest and largest packaging configuration will be placed on stability at 30°C/75% RH. At least one production batch each year will be placed on stability at 30°C/75% RH.

The applicant requests a categorical exclusion from the requirement to prepare an Environmental Assessment.

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

Zidovudine 60 mg tablets alone or in combination with other antiretroviral agents are indicated for the treatment of HIV-1 infection. The recommended dose for pediatric patients is 1-5 tablets (depending on patient weight) taken twice daily. The tablets are

supplied in 40 cc [redacted] bottles containing 60 tablets, 120 cc bottles containing 1000 tablets, blister packs of 10,[redacted] The storage statement is: "Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]" and the expiration dating period is 24 months. b(4)

C. Basis for Approvability or Not-Approval Recommendation

The chemistry, manufacturing, and controls for the zidovudine drug substance is described in DMF 18714, as amended. The DMF has been reviewed and found to be satisfactory. The composition, manufacturing process, and specifications for the zidovudine tablets are appropriate and the expiration dating period of 24 months is supported by adequate data. The container-closure system and labeling are appropriate. The manufacturing sites have been found to be acceptable. This NDA is therefore recommended for approval from the CMC perspective.

III. Administrative

A. Reviewer's Signature

/s/ H. Ted Chang, Ph.D.

/s/ Stephen P. Miller, Ph.D.

B. Endorsement Block

CMC Reviewer:	H. Ted Chang, Ph.D.
Pharmaceutical Assessment Lead:	Stephen P. Miller, Ph.D.
Branch Chief:	Norman R. Schmuff, Ph.D.
Project Manager:	Monica Zeballos

C. CC Block

Orig. NDA 22-294
HFD-530/Division File

57 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry Review Section- B