

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

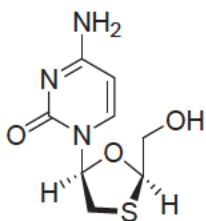
APPLICATION NUMBER:

022018Orig1s000

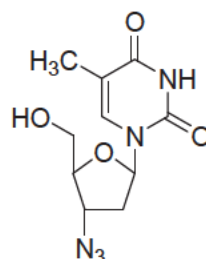
PRODUCT QUALITY REVIEW(S)

NDA 22018 Orig-1 Resub-16

Lamivudine and Zidovudine Tablets



Lamivudine (150 mg)



Zidovudine (300 mg)

Applicant: Pharmicare Limited

Summary:

NDA 22018 was tentatively-approved under PEPFAR program in August 2006. The applicant now is seeking a final approval in USA. Lamivudine drug substance is manufactured and supplied by (b) (4)

Zidovudine drug substance is manufactured and supplied by (b) (4)

The CMC information for the drug substances was cross-referenced to the corresponding DMF (b) (4) (Lamivudine), DMF (b) (4) (Zidovudine) and DMF (b) (4) (Zidovudine). Up to date, DMF (b) (4) and DMF (b) (4) are deemed adequate from CMC quality perspective. The recent amendment of DMF (b) (4) (Zidovudine) submitted on 01/06/2017 was reviewed by Barbara Scott and deemed adequate with additional comments. An information request letter was sent to the DMF holder on 01/23/2017.

The drug product is an immediate release oral tablet. Each tablet contains 150 mg of lamivudine and 300 mg of zidovudine as active ingredients and the following excipients: microcrystalline cellulose (b) (4), sodium starch glycolate (b) (4), hypromellose (b) (4), magnesium stearate (b) (4) and colloidal silicon dioxide (b) (4). Drug product is manufactured by Aspen Port Elizabeth (Pty) Ltd (FEI# 3003692704).

The facilities manufacturing drug substance and drug product are currently recommended to approve (Panorama Date: Feb 3, 2016).

No Biopharm or Process reviews were needed. Refer to the NDA 22018 filing review by Stephen Miller.

Review the response to IR sent on 03-Nov-2016

1. The current Drug Product Specification (in 3.2.P.5).

Applicant's response: Satisfactory

The current drug product specification has been submitted in 3.2.P.5.1. This is the same specification as that in the supplement-1 dated 08/26/2014.

2. *Clarification of whether* [redacted] (b) (4) *according to our records was present in 2006.*

Applicant's response: Satisfactory

The applicant confirms that [redacted] (b) (4)

3. *An overview of the changes made since NDA 22018 received tentative approval in 2006.*

Applicant's response: Satisfactory

The applicant has provided an overview of the changes made since tentative approval in 2006 as summarized in the table below.

Overview of Changes made since Tentative Approval in August 2006

Amendment Date	Details of Amendment	FDA Response	Aspen Pharmacare Comment
March 19, 2012	Change in US Agent to Lachman Consultant Services, Inc	-	
August 26, 2014	Labeling updated in line with latest RLD labeling	Feb 03, 2015: General Advice Letter: Submit the proposed labeling change as a separate submission and in the correct format: - conversion of the package insert to comply with the PLR requirement	Response to FDA letter submitted on March 17, 2015
	Addition of a new drug substance manufacturing site (b) (4)	Permitted Sep 17, 2015	-
	Minor change in formulation (b) (4) (b) (4)	Permitted Sep 17, 2015	-
	Minor changes in processing parameters (change in (b) (4))	Permitted Sep 17, 2015	-
	Manufacturing process updated in line with the original validation report in the NDA submission.		
	Updated DP manufacturer drug substance and excipient specifications in line with USP	Nov 20, 2014: E-mail Information Request (b) (4)	Response to FDA e-mail submitted on Dec 11, 2014.

Amendment Date	Details of Amendment	FDA Response	Aspen Pharmacare Comment
August 26, 2014 (continued)	Update of drug product specifications/method of analysis: (b) (4) - change in dissolution specification/method of analysis and validation provided - change in related substances specifications/ method of analysis and validation provided (b) (4) - Assay method updated to USP & validation provided Change in packaging material from (b) (4)	Permitted Sep 17, 2015 Nov 20, 2014: E-mail Information Request Please clarify if the materials of construction for the desiccant disc (b) (4) (b) (4) provide a statement from the supplier to confirm. If not, provide data/justification to demonstrate that the safety of the proposed desiccant disc when in contact with your drug product.	(b) (4) Response to FDA e-mail submitted on Dec 11, 2014. Request for 24 month shelf-life was included in the comparison table attached to our cover letter of Aug 2014. Request for 24 month shelf-life was resubmitted in Final approval request of Sep 17, 2016, as the Aug 2006 FDA tentative approval letter specified as (b) (4) shelf-life.
Dec 11, 2014	Response to FDA query dated Nov 20, 2014 regarding (b) (4) - inactive pharmaceutical specifications: comparison table provided - desiccant disc: declaration regarding US FDA food (b) (4)	Dec 12, 2014: E-mail Information Request Provide a site to site comparison table for the approved and the proposed Zidovudine specification. Provide justification(s) for any deviation from the approved specification.	Response to FDA e-mail submitted on Dec 17, 2014.

Amendment Date	Details of Amendment	FDA Response	Aspen Pharmacare Comment
Dec 17, 2014	Response to FDA e-mail dated Dec 12, 2014: Zidovudine comparison table provided: DP manufacturer vs DS manufacturer (b) (4) removed from the application as DS supplier.	Permitted Sep 17, 2015	
		Dec 24, 2014: PEPFAR Amendment Denied: (b) (4)	Response to FDA letter submitted on March 16, 2015.
March 16, 2015	Response to FDA letter dated Dec 24, 2014: (b) (4)	Permitted Sep 17, 2015 Submit stability data with the new desiccant when available via an "Annual Update" submission.	
March 17, 2015	Response to FDA General Advice Letter dated Feb 03, 2015: - package insert submitted in PLR format	No response.	
Sep 16, 2016	Request for final approval: - 1.14: Updated package insert and labeling - 3.2.S.2.1 (Lamivudine and Zidovudine) Amend address of (b) (4) - 3.2.P.1 Correct typographical error in the formulation (Hyromellose quantity) - 3.2.P.3.1 Update contact details for DP manufacturer - 3.2.P.8: submit updated stability data and request 24 month expiration dating period - 5.3.1.3: submit amended comparative dissolution reports	Pending	

NDA 22-018 for lamivudine /zidovudine Tablets, 150 mg/300mg, was tentatively-approved under PEPFAR program in August 2006. The first amendment (Suppl-1) was submitted on 26 Aug 2014. (b) (4)

(b) (4)

The applicant submitted formal NDA on September 16, 2016.

There are no CMC related changes in the final NDA since issuing the PEPFAR permitted action letter.

4. *Verification that the intended packaging configuration will use the same materials and suppliers as submitted in the amendment dated Aug 26, 2014 and subsequent amendments (HDPE bottle, Child-Resistant cap, induction seal, desiccant disc). Clarify whether any stability data are available with the desiccant disc supplied by (b) (4), as noted in the PEPFAR Amendment Permitted letter of Sept 17, 2015.*

Applicant's response: Satisfactory

The applicant confirms that the intended packaging configuration will use the same materials and suppliers as submitted in the amendment dated Aug 26, 2014 and subsequent amendments (shown below). Batches have not yet been manufactured using the new equivalent desiccant supplier. Therefore, stability data are not yet available with the desiccant disc supplied by (b) (4). The applicant commits to submit stability data with the new desiccant via an "ANNUAL UPDATE" when data is available.

Xinghua Wu, Ph.D.

CMC reviewer

03/17/2017

Date

Stephen P. Miller, Ph.D.

CMC-Lead

See Panorama

Date

DRUG PRODUCT

Product Background:

NDA: 22018

Drug Product Name / Strength: Lamivudine (150 mg) and Zidovudine (300 mg)
Tablet

Route of Administration: Oral

Applicant Name: Pharmacare Limited

Review Recommendation:

From the CMC perspective, NDA 22018 is recommended for approval. This recommendation is for the following:

- 1) Manufacture of the Lamivudine/Zidovudine Tablets, 150 mg/300 mg, by the proposed commercial method described in the NDA submission and amendments.
- 2) The lamivudine/zidovudine tablets (60 tablets) are packed in the HDPE bottle with a desiccant disc, a child resistant white (b)(4) cap and a heat seal liner
- 3) An expiration period of 24 months is granted when stored between 2°C and 30°C (36°F - 86°F) and protected from moisture and light.

Review Summary:

NDA 22018 was granted a tentative approval for the treatment of patients with HIV infection under the PEPFAR program in August 2006. The commercial tablets, Lamivudine (150 mg)/Zidovudine (300 mg), (b)(4)

The applicant submitted a NDA approval request on September 17, 2016 to market the drug product in USA.

List of submissions being reviewed:

Type of Submission	Date of Submission	SD Number
Original (PEPFAR)	02/16/2006	1
Amendment	03/14/2016	3
Amendment	05/17/2006	4
Amendment	08/01/2006	5
Amendment	08/16/2006	6
Amendment	08/21/2006	7
Suppl-1	08/26/2014	12
Suppl-1 (Resubmission)	03/16/2015	13
Suppl-1	09/17/2015	14
NDA approval request	09/17/2016	16
Amendment	11/08/2016	17

Type II DMF	Drug substance	Status/Date
(b) (4)	Lamivudine USP	Adequate/24-Feb-2017
	Zidovudine	Adequate/25-Feb-2015
	Zidovudine	Information request sent on 23-Jan-2017
	Zidovudine	Adequate/16-Mar-2017

P.1 Description and Composition

Lamivudine (150 mg) and Zidovudine (300 mg) tablets are white to off-white, slightly mottled, oval biconvex (b) (4) tablets with bevelled edges and debossed with "E57" on the one side.

(b) (4)

Component/composition table

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Labeling Evaluation

Highlights of Prescribing Information:

LAMIVUDINE and ZIDOVUDINE TABLETS, 150 mg/300 mg

Note: this change should be made throughout the prescribing information and on the bottle label.

-----DOSAGE FORMS AND STRENGTHS-----

Tablets: 150 mg lamivudine and 300 mg zidovudine (3)

1 DOSAGE AND ADMINISTRATION

1.1 Recommended Dosage for Adults and Adolescents

The recommended dosage of Lamivudine/Zidovudine Tablets in HIV-1-infected adults and adolescents weighing greater than or equal to 30 kg is 1 tablet (containing 150 mg of lamivudine and 300 mg of zidovudine) taken orally twice daily

Main Text of Prescribing Information:

1 DOSAGE FORMS AND STRENGTHS

Lamivudine/Zidovudine Tablets contain 150 mg of lamivudine and 300 mg of zidovudine. The tablets are white to off-white, slightly mottled, oval biconvex with bevelled edges and debossed with “E57” on the one side.

10 DESCRIPTION

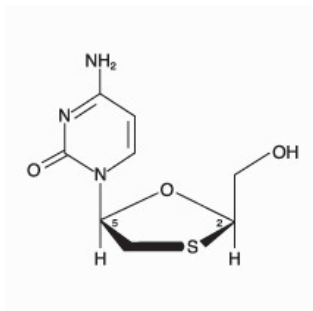
Lamivudine/Zidovudine Tablets are combination tablets containing lamivudine and zidovudine. Lamivudine (EPIVIR) and zidovudine (RETROVIR, azidothymidine, AZT, or ZDV) are synthetic nucleoside analogues with activity against HIV-1.

Lamivudine/Zidovudine Tablets are for oral administration. Each tablet contains 150 mg of lamivudine, 300 mg of zidovudine, and the inactive ingredients colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, sodium starch glycollate, and talc..

Lamivudine

The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)- (1H)-pyrimidin-2-one. Lamivudine is the (-)-enantiomer of a dideoxy analogue of cytidine.

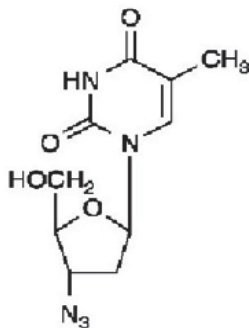
Lamivudine has also been referred to as (-)-2',3'-dideoxy, 3'-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.3 g per mol. It has the following structural formula:



Lamivudine is a white to off-white crystalline solid and is soluble in water.

Zidovudine

The chemical name of zidovudine is 3'-azido-3'-deoxythymidine. It has a molecular formula of C₁₀H₁₃N₅O₄ and a molecular weight of 267.24 g per mol. It has the following structural formula:



Zidovudine is a white to beige, odorless, crystalline solid with a solubility of 20.1 mg per mL in water at 25°C.

16 HOW SUPPLIED/STORAGE AND HANDLING

Lamivudine/Zidovudine Tablets, containing 150 mg lamivudine and 300 mg zidovudine, are white to off-white, slightly mottled, oval biconvex with bevelled edges and debossed with "E57" on the one side. They are available as follows:

60 Tablets/Bottle with desiccant, induction seal and child-resistant cap (NDC 52719-760-59).

Store between 2°C and 30°C (36°F - 86°F). Protect from moisture and light.

Patient Instructions (if used): none in this case

Bottle Label:

(b) (4)

Carton Label: none

Labeling Recommendations:

- 1) In consideration of the USP Monograph, and the demonstrated stability of your tablets under long-term stability studies at 30°C/75%RH, we recommend that the storage statements in Section 16 and on the bottle label be modified to read:
“Store between 2°C and 30°C (36°F - 86°F). Protect from moisture and light.”
- 2) Please revise the name of the product on the bottle label and throughout the prescribing information to read: “Lamivudine and Zidovudine Tablets”
- 3) Please modify the list of inactive ingredients in Section 10 to be in alphabetical order:
“Each tablet contains 150 mg of lamivudine, 300 mg of zidovudine, and the inactive ingredients colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, sodium starch glycollate, and talc.”
- 4) Please modify the statement in Section 16 to read: “60 Tablets/Bottle with desiccant, induction seal and child-resistant cap (NDC 52719-760-59).”



Stephen
Miller

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Xinghua
Wu

Digitally signed by Xinghua Wu
Date: 3/17/2017 09:33:14AM
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Office of Pharmaceutical Quality
NDA Reviewer Assignment Information

NDA #: 22018 –Orig-1-Resub-16	Established/Proper Name: Lamivudine and Zidovudine Tablets
Dosage Form: IR tablet	Strengths: 150 mg/300 mg
Applicant: Aspen Pharmacare, Ltd.	Lead Branch: Branch III, DNDP-1, ONDP
BCS Class: high solubility	Approximate Goal Date for Primary Review: NA
Submission Type: b2 (PEPFAR)	Goal Date for Action: Mar 19, 2017
Chemical Type: 4	Cross Referenced Applications: the 356h lists DMF (b) (4) for Lamivudine (b) (4) DMF (b) (4) and DMF (b) (4) for Zidovudine (b) (4). These 3 DMFs were also included in S-001 and therefore covered by the PEPFAR Permitted Letter of Dec 2015.

Office of Pharmaceutical Quality

NDA Reviewer Assignment Information

This submission requests conversion of this NDA from Tentative Approval to Full Approval, now that expiration of patents allows marketing in the US. It is the first electronic submission of product quality information for this NDA, although some prescribing information and container labeling from 2014 is available through DARRTS.

Tentative Approval was granted in Aug 2006. An amendment (“Suppl-1”) was submitted in Aug 2014 which included significant changes:

- 1) addition of a new manufacturing site ((b) (4)) for both lamivudine and zidovudine (b) (4)
- 2) minor change to the formulation ((b) (4) },
- 3) minor change in manufacturing process (b) (4)
- 4) specifications for API (b) (4) updated in line with the latest pharmacopoeia
- 5) specifications for the finished product updated in line with the latest pharmacopoeia (the acceptance criterion for appearance on the DP specification (b) (4) present in 2006).
- 6) change in packaging material (b) (4) to HDPE bottles with a (b) (4) cap

A PEPFAR Permitted action letter was issued for Suppl-1 (as amended) in Dec 2015 (see Panorma). This action was supported by a CMC review and a Biopharm review (which noted the upgraded dissolution method and acceptance criteria: $Q = \frac{(b) (4)}{(4)}\%$ for each active at $\frac{(b) (4)}{(4)}$ min ($Q = \frac{(b) (4)}{(4)}\%$); (b) (4)

The Sept 2016 “Resub-16” submission included manufacturing facility information, DP composition, stability data on batch A303947 (manuf Sept 2013) and comparative stability data from “Initial Submission Batches” (manuf 2002 and 2005) and labeling. In response to an information request, the Nov 2016 amendment also provided the current DP specification, clarification (b) (4) an overview of changes made since the NDA was tentatively approved in 2006, and clarification regarding packaging.

The current recommendation from the Division of Antiviral Drugs is that this product (b) (4) See the email trail below for additional background.

Recommendations: This application is complete for filing. Given that the original NDA was reviewed pre-OPQ, a complete set of reviews (IQA) is not necessary for this resubmission. The following review assignments are recommended:

- DP and Labeling – Xinghua Wu is assigned
- Biopharm – BP BC confirmed that BP review is not necessary
- Process – Process BC confirmed that Process review is not necessary
- Facilities – per BC input, manuf facilities will be evaluated and results conveyed via Submission Facility Status View, without a separate written review.

Office of Pharmaceutical Quality

NDA Reviewer Assignment Information

Attachment 1 – Drug Product Specification from Full Approval Amendment

(As submitted in the Nov 8, 2016 amendment)

	PROPOSED	Page 2 of 38
	FINISHED PRODUCT SPECIFICATIONS AND METHODS OF ANALYSIS	
	Confidential Document	
Item No.: 382760	Issue No.: 1	
Product: Lamivudine 150 mg and Zidovudine 300 mg Tablets	Project No.: (b) (4)	

TEST	SPECIFICATION	TEST STAGE
APPEARANCE	A white to off-white granule. A white to off-white, slightly mottled, oval, biconvex tablet with bevelled edges and debossed with E57 on the one side.	(b) (4)
IDENTIFICATION Lamivudine Zidovudine	In the assay method employed, the HPLC retention times of the drug actives as obtained in the sample chromatogram correspond to those obtained in the standard chromatogram.	(b) (4)
AVERAGE MASS	700.0 mg (665.0 mg to 735.0 mg).	(b) (4)
UNIFORMITY OF MASS		(b) (4)
AVERAGE HARDNESS^v (Lengthwise)		(b) (4)
LENGTH	15.5 mm (14.7 mm to 16.3 mm).	(b) (4)
WIDTH	7.8 mm (7.4 mm to 8.2 mm).	(b) (4)
THICKNESS^v	6.5 mm (5.9 mm to 7.2 mm).	(b) (4)
FRIABILITY		(b) (4)
DISINTEGRATION		(b) (4)
MOISTURE		(b) (4)
DISSOLUTION Lamivudine Zidovudine	Not less than (b) (4)% of lamivudine is released within (b) (4) (Q = (b) (4)%). Not less than (b) (4)% of zidovudine is released within (b) (4) (Q = (b) (4)%).	(b) (4)

Continued

**Office of Pharmaceutical Quality
NDA Reviewer Assignment Information**

**Attachment 1 – Drug Product Specification from Full Approval Amendment
(page 2)**

TEST	SPECIFICATION	TEST STAGE
RELATED SUBSTANCES Lamivudine impurities		(b) (4)
	(b) (4)	
Total lamivudine related impurities with respect to lamivudine	(b) (4)	
Zidovudine impurities		
	(b) (4)	
Individual unidentified impurities with respect to zidovudine	(b) (4)	
Total zidovudine related impurities (including individual unidentified impurities) with respect to zidovudine	(b) (4)	
UNIFORMITY OF DOSAGE UNITS		(b) (4) (b) (4)
	(b) (4)	
Lamivudine and Zidovudine		
ASSAY		(b) (4)
mg Lamivudine per tablet		
mg Zidovudine per tablet		

ORIGINAL

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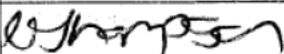
Office of Pharmaceutical Quality NDA Reviewer Assignment Information

Attachment 1 – Drug Product Specification from Full Approval Amendment (page 3)

TEST	SPECIFICATION	TEST STAGE
MICROBIAL LIMITS		(b) (4)
Total Aerobic Microbial Count (TAMC)	Not more than (b) (4) cfu/g.	
Total Combined Yeasts and Mould (TYMC)	Not more than (b) (4) cfu/g.	
Escherichia coli	Absence of Escherichia coli per g.	
		(b) (4)

- * For information only – performed in IPC laboratory.
- ** Not for registration purposes, for information only.
- ¥ Provisional – limit to be confirmed.
- ✖ To be performed at the beginning and end of shelf-life.

ORIGINAL

	Prepared by Specifications Department	Reviewed by Validation Department
Name	C. Thompson	B. Simpson
Date	27 Nov 2013	29 Nov 2013
Signature		

Office of Pharmaceutical Quality
NDA Reviewer Assignment Information

Attachment 2 – Drug Product Specification from S-001

(From CMC Review-1 of Supplement-1; Dec 2014)

TEST	SPECIFICATION	TEST STAGE
APPEARANCE	A white to off-white granule. A white to off-white, slightly mottled, oval, biconvex tablet with bevelled edges and debossed with E57 on the one side.	(b) (4)
IDENTIFICATION Lamivudine Zidovudine	In the assay method employed, the HPLC retention times of the drug actives as obtained in the sample chromatogram correspond to those obtained in the standard chromatogram.	
AVERAGE MASS	700.0 mg (665.0 mg to 735.0 mg).	
UNIFORMITY OF MASS		
AVERAGE HARDNESS^Y (Lengthwise)		
LENGTH	15.5 mm (14.7 mm to 16.3 mm).	
WIDTH	7.8 mm (7.4 mm to 8.2 mm).	
THICKNESS^Y	6.5 mm (5.9 mm to 7.2 mm).	
FRIABILITY		
DISINTEGRATION		
MOISTURE		
DISSOLUTION Lamivudine Zidovudine	Not less than (b) (4) % of lamivudine is released within (b) (4) (Q = (b) (4) %). Not less than (b) (4) % of zidovudine is released within (b) (4) (Q = (b) (4) %).	

Continued

Office of Pharmaceutical Quality
NDA Reviewer Assignment Information

Appendix 2 - Drug Product Specification from S-001 (page 2)

TEST	SPECIFICATION	TEST STAGE
RELATED SUBSTANCES Lamivudine impurities		(b) (4)
	(b) (4)	ORIGINAL
Total lamivudine related impurities with respect to lamivudine	(b) (4)	
Zidovudine impurities	(b) (4)	
compound C (Thymine)	(b) (4)	
Individual unidentified impurities with respect to zidovudine	(b) (4)	
Total zidovudine related impurities (including individual unidentified impurities) with respect to zidovudine	(b) (4)	
UNIFORMITY OF DOSAGE UNITS	(b) (4)	(b) (4)
	(b) (4)	
Lamivudine and Zidovudine		
ASSAY		
mg Lamivudine per tablet		
mg Zidovudine per tablet		

Continued

**Office of Pharmaceutical Quality
NDA Reviewer Assignment Information**

Appendix 2 - Drug Product Specification from S-001 (page 3)

TEST	SPECIFICATION	TEST STAGE
MICROBIAL LIMITS		
Total Aerobic Microbial Count (TAMC)	Not more than (b) (4) cfu/g.	(b) (4)
Total Combined Yeasts and Mould (TYMC)	Not more than (b) (4) cfu/g.	
Escherichia coli	Absence of Escherichia coli per g.	
(b) (4)		

- * For information only – performed in IPC laboratory.
- ** Not for registration purposes, for information only.
- ¥ Provisional – limit to be confirmed.
- ¤ To be performed at the beginning and end of shelf-life.

ORIGINA

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Office of Pharmaceutical Quality

NDA Reviewer Assignment Information

NDA 22018:

Orig Rev (Aug 2006): The tablets are white to off-white, (b) (4) slightly mottled, 15.5mm x 7.8 mm (6 mm thick), oval, (b) (4) bevelled (b) (4) tablets with (b) (4) imprinted and (b) (4) on one side (total wt 700 mg).

Sept 2016 Submission (3.2.P.1 and stability data on batch A303947; manuf Sept 2013): Lamivudine/Zidovudine Tablets, 150 mg/300 mg are white to off-white, slightly mottled, oval biconvex tablet with bevelled edges and debossed with “E57” on the one side.

Sept 2016 Submission (Stability data on “Initial Submission Batches” manuf 2002 and 2005): there is no mention (b) (4) in the appearance specification.

Action: last week we have sent Aspen several questions, including whether the Lamivudine and Zidovudine tablets that are proposed for full approval (b) (4).

Steve



Stephen
Miller

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NDA #22-018

**Lamivudine/Zidovudine Tablets
150 mg/300mg**

**Pharmacare Limited
Johannesburg, South Africa**

**CMC Review
Rao V. Kambhampati, Ph.D.
Senior Regulatory Review Scientist
ONDQA, DPA II, Branch IV**

Chemistry Review Data Sheet

1. NDA# **22-018**
2. REVIEW #: 1
3. REVIEW DATE: 8/18/2006
4. REVIEWER: Rao V. Kambhampati, Ph.D.
5. PREVIOUS DOCUMENTS: N/A
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original N 000	2/16/06
Amendment N 000 BL	3/14/06
Amendment N 000 AC	5/17/06
Amendment N 000 BZ	8/1/06
Amendment N 000 BC	8/4/06
Amendment N 000 BL	8/7/06

7. NAME & ADDRESS OF APPLICANT:

Name:	Pharmacare Limited t/a Aspen Pharmacare
Address:	Building 12, Healthcare Park Woodlands Drive Woodmead, Johannesburg, 2158 South Africa
U.S. Representative:	ShorePharm LLC Attn: Mark Moshier/Keith Giunta 76 South Orange Avenue, Suite #203 South Orange, NJ 07079
Telephone:	27 11 239 6327 (Pharmacare), 973-761-1600 (Shore Pharm)

8. DRUG PRODUCT NAME/CODE/TYPE:
 - a) Proprietary Name: N/A
 - b) Non-Proprietary Name: Lamivudine/Zidovudine tablets, 150 mg/300 mg
 - c) Code Name/#: N/A
 - d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 4
 - Submission Priority: S
 - Fast-Track: Yes
 - PEPFAR: Yes
9. LEGAL BASIS FOR SUBMISSION: N/A
10. PHARMACOL CATEGORY: Antiviral

Chemistry Review Data Sheet

11. DOSAGE FORM: Tablets
12. STRENGTH/POTENCY: Each tablet contains 150 mg of lamivudine and 300 mg of zidovudine
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:

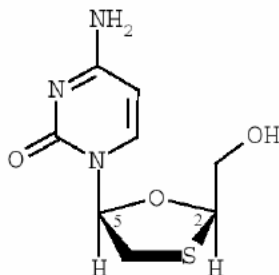
Lamivudine:

Chemical Name: (-) 2',3'-dideoxy-3'-thiacytidine

CAS Reg. No.: 134678-17-4

Molecular Formula: C₈H₁₁N₃O₃SMolecular Weight: 229. ^{(b) (4)}

Structural Formula:

Zidovudine:

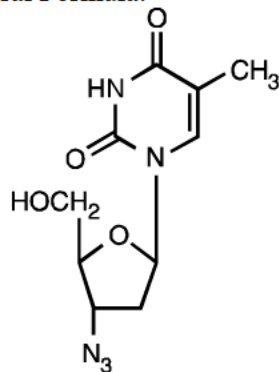
Chemical Name: 3'-Azido-3'-deoxythymidine

CAS Reg. No.: 30516-87-1

Molecular Formula: C₁₀H₁₃N₅O₄

Molecular Weight: 267.24

Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS: N/A

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	Review	COMMENTS
(b) (4)	II		(b) (4)	Yes	Adequate
	II			Yes	Adequate
	II			Yes 12/13/04 (review 1) 2/18/05 (review 2) 7/13/05 (review 3) 5/22/06 (review 4)	Adequate
	II			Yes 11/16/04 (review 1) 3/4/05 (review 2) 7/13/05 (review 3)	Adequate
	II			Yes 5/25/06 (review 4)	Adequate

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	(b) (4)	(b) (4)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EER	Acceptable	6/1/06	S. Adams (HFD-322, DMPQ), OC
Trademark Review	N/A	N/A	N/A
EA	Acceptable (Categorical Exclusion)	7/5/06	Rao V. Kambhampati, Ph.D.
Clin-Pharm Review for suitability of PK studies and reference materials	Acceptable	8/18/06	Vikram Arya, Ph.D.
Methods Validation	Not Necessary	7/5/06	Rao V. Kambhampati, Ph.D.

The Chemistry Review for NDA 22-018

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls (CMC) standpoint, the NDA #22-018 is recommended for tentative approval. This recommendation is for the following:

- 1) Manufacture of the Lamivudine/Zidovudine Tablets, 150 mg/300 mg, by the proposed commercial method described in the NDA submission and amendments there to.
- 2) The lamivudine/zidovudine tablets are packaged in [REDACTED] (b) (4)
- 3) An expiration dating period of [REDACTED] (b) (4)

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

N/A

II. Summary of Chemistry Assessments

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

The Applicant, Pharmacare Limited (aka Aspen Pharmacare, Johannesburg, South Africa) intends to seek tentative approval of the FDA under PEPFAR program for Lamivudine/Zidovudine Tablets, 150 mg/300 mg, for the treatment of patients with HIV infection. The commercial tablets are packaged [REDACTED] (b) (4)

[REDACTED] Lamivudine and zidovudine are known molecular entities and these drug substances were approved by the FDA for their use in brand name tablets, Combivir (GlaxoSmithKline) as well as in generic tablets.

Drug Substances:

Zidovudine drug substance is manufactured and supplied by [REDACTED] (b) (4)

[REDACTED] Lamivudine drug substance is manufactured and supplied

Executive Summary Section

by (b) (4). The CMC information for the drug substances was cross-referenced to the corresponding DMFs and amendments there to and Letters of Authorization (LOAs) were provided in the NDA for the cross-reference of the CMC information in the DMFs. All four DMFs were reviewed and found to be adequate by the ONDQA chemists (DMFs (b) (4) and (b) (4) by Cheng Yi Liang, Ph.D. and DMFs (b) (4) and (b) (4) by George Lunn, Ph.D.).

Drug Product:

The drug product is immediate release oral tablet. The tablets are white to off-white, slightly mottled, 15.5mm x 7.8 mm, oval, (b) (4) bevelled (b) (4) tablets with (b) (4) imprinted and (b) (4) on one side. Each tablet (total wt 700 mg) contains 150 mg of lamivudine and 300 mg of zidovudine as active ingredients and the following excipients: sodium starch glycolate (b) (4), microcrystalline cellulose (b) (4), talc (b) (4), magnesium stearate (b) (4), and colloidal silicon dioxide (b) (4).

The formulation is based on an (b) (4) generic product manufactured by (b) (4). The developmental batches were manufactured by Pharmaceutical Research Laboratories (PRL), a division of Aspen Pharmacare located at the manufacturing site at Port Elizabeth, Republic of South Africa. The larger scale batches were manufactured at the (b) (4) facility and the intended commercial scale batches were manufactured at the (b) (4) facility. (b) (4). The PRL and (b) (4) facility batches involve (b) (4) method for the lamivudine component whereas the (b) (4) batches involve (b) (4) method. Therefore, the (b) (4) batches are considered as representative commercial batches. The (b) (4) manufacturing process involves (b) (4).

The proposed release specifications for the intended commercial process (b) (4) batches included appearance, identity of lamivudine and zidovudine by HPLC, moisture content, average mass, disintegration, hardness, length, width, thickness, friability, uniformity of mass, dissolution of lamivudine and zidovudine, degradation products/impurities (b) (4) other individual, and total), and assay for

Executive Summary Section

lamivudine and zidovudine. The proposed stability specifications for the commercial product included appearance, hardness, friability, disintegration, moisture, degradation products/impurities, assay, and dissolution. Upon comment, comparative batch analysis data were provided in the amendment (8/4/06) for eight batches (two development, two (b) (4) facility, and four proposed commercial (b) (4) facility). However, four of the eight batches are considered as representative commercial process batches because of the change in the method (b) (4)



In the original NDA submission, the stability data were provided for six batches. In the amendment dated 8/4/06, data were provided for 8 batches which included an update of the previously submitted 6 batches. Of the eight batches, the two development batches (300275 and 300277) and two (b) (4) facility batches (E163680 and E163681) were packaged (b) (4)



Executive Summary Section

(b) (4)

The applicant initially proposed (b) (4) as the trade name for lamivudine/zidovudine combination tablets, 150 mg/300 mg, however, the DAVP advised the Applicant that the proposed trade name is not acceptable, therefore, the tablets will be marketed as Lamivudine/Zidovudine Tablets, 150 mg/300 mg, upon approval. The established names for the drug substances, lamivudine and zidovudine, are approved USAN names. Some changes were recommended to the proposed package insert (b) (4)

The three drug substance manufacturing facilities (b) (4) and the commercial manufacturing, packaging, lot release, and stability testing facility for the tablets (Aspen Pharmacare, Port Elizabeth, South Africa) were found to be acceptable on the basis of the file review by the DMPQ (HFD-324), OC. The dissolution methods including the acceptance criteria for the tablets are acceptable from the CMC stand point and from the Clin-Pharm perspective (Vikram Arya, Ph.D., 8/18/06). According to the recent ONDQA policy, the analytical methods validation for this NDA is not required. The applicant's request for an exemption from the EA requirement under categorical exclusion is acceptable (per FDA policy decision, 1/19/05).

III. Administrative

- **A. Reviewer's Signature**

Signed electronically in DFS by Rao V. Kambhampati, Ph.D., Senior Regulatory Review Scientist, Branch IV, DPA II, ONDQA

- **B. Endorsement Block**

Signed electronically in DFS by Norman Schmuff, Ph.D., Branch Chief, Branch IV, DPA II, ONDQA

- **C. CC Block**

Org. NDA 22-018	HFD-800/SRRS/RKambhampati
HFD-800/Branch Chief/NSchmuff	HFD-800/PAL/SMiller
HFD-800/PM/LAthey	HFD-530/PM/VReddy

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Chemistry Assessment Section

C. INVESTIGATIONAL FORMULATIONS

Information regarding investigational formulations was provided in the Pharmaceutical Development Section of the Drug Product.

D. ENVIRONMENTAL ASSESSMENT

The applicant submitted the following statement:

Approval of this NDA will not increase the use of the active moieties and, therefore, this action is categorically excluded under 21CFR 25.31(a) from the need to submit an environmental assessment. To our knowledge, no extraordinary circumstances (as described in 21CFR 25.21) exist.

Comments: *This is consistent with the FDA policy discussion of January 19, 2005.*

E. METHODS VALIDATION

Both the lamivudine and zidovudine drug substances are known in the literature and are manufactured by the known synthetic routes. The lamivudine/zidovudine tablets are manufactured (b) (4) facilities. The methods used either conform to USP or EP except HPLC method used for the determination of Assay and Impurities/Degradation Products content. A Method Validation Report was provided for the HPLC methods and they are acceptable. Based on the information provided in the NDA, it seems reasonable to conclude that a Method Validation by the FDA lab is not necessary at this point.

Comments: Acceptable

F. LABELING

a) Package Insert: Some changes were recommended to the name of drug, Description section, and How Supplied section of the initially submitted package insert. These changes were accepted by the Applicant. A revised package insert was submitted in the amendment dated 8/7/06 with all the recommended changes.

Comments: *The revised PI dated 8/7/06 is acceptable. See Draft Deficiency Letter (H) of this review for more information.*

b) (b) (4) Carton Labels: Several changes were recommended to the initially submitted mock (b) (4) carton label. The recommended changes were accepted by the Applicant and the final revised mock (b) (4) carton label were submitted in the amendment dated 8/7/06. The final revised labels and the initial draft labels are provided below:

Final Revised Labels:

Chemistry Assessment Section

(b) (4)

Chemistry Assessment Section

(b) (4)

Overall Comments: *The applicant agreed to all the proposed changes to the initially submitted mock (b) (4) carton labels. The final printed documents will reflect those changes. The name (b) (4) was changed to "Lamivudine/Zidovudine Tablets, 150 mg/300 mg". See Draft Deficiencies Letter (H) of this review for more information...*

G. ESTABLISHMENT INSPECTION

An acceptable overall recommendation was issued by Ms. S. Adams (HFD-322, DMPQ, OC) on 6/1/06.

Comments: *Acceptable. The three drug substance manufacturing facilities (b) (4) and the drug product manufacturing facility (Pharmacare) were inspected previously, therefore, an Overall Recommendation of Acceptable was issued by DMPQ on the basis of the file review*

H. DRAFT DEFICIENCY LETTER

Note: The following comments were communicated to the applicant by telefacsimiles on 7/7/06 and the applicant satisfactorily addressed them in the amendment dated 8/4/06.

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

/s/

Rao Kambhampati
8/18/2006 08:13:15 PM
CHEMIST
Recommended for Approval.
Please sign off and file.

Norman Schmuff
8/22/2006 12:10:58 PM
CHEMIST

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 22- 018

DRUG: Fixed Dose Combination of Lamivudine/Zidovudine

INDICATION: Treatment of HIV Infection

APPLICANT: Aspen

OCPB Division: DCP4

OND Division: Division of Antiviral Products

SUBMISSION DATE: February 24, 2006

REVIEWER: Vikram Arya, Ph.D.

TEAM LEADER: Kellie Reynolds, Pharm.D.

Aspen Pharmacare (sponsor) submitted a New Drug Application for the fixed dose combination of Lamivudine/Zidovudine (150 mg/300 mg). This application was submitted under the Presidents Emergency Plan for AIDS Relief (PEPFAR) initiative.

Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the information submitted in this NDA and concludes that the information provided is acceptable.

Summary

In support of the application, the sponsor submitted the results of the following bioequivalence study:

SACT 25/2002

A single dose, laboratory blinded, randomized, two-part cross-over study to determine bioequivalence of a lamivudine and zidovudine fixed-dose combination product with respect to an innovator product. The results of this study were previously submitted (b) (4)

The concentration-time data and the pharmacokinetic parameters of zidovudine were similar between the two NDA's, however, a comparison of the concentration-time data and the pharmacokinetic parameters of lamivudine (b) (4) 22-018) showed some differences. The sponsor stated that the discrepancies, in part, were due to the differences between the original statistical report (b) (4) and the analytical report (version 11, March 2003). The original statistical report presented the pharmacokinetic parameters of lamivudine based on the preliminary data but the analytical report (as addendum April 14, 2003) contained the final lamivudine concentrations. However, even after taking the updated study report into consideration, there were still some discrepancies in the data. The sponsor was requested to clarify the discrepancies listed below (in italics; the sponsor's response is in bold). The clarification was requested because approval of this product was based on one BE study, so data integrity is essential.

Lamivudine Test Formulation

1. For subject 21, the concentration at 36 hours reported in this NDA (b) (4) were different, however, the AUC estimates are identical.

The sponsor stated that the plasma concentrations listed at 36 hr after dosing of the test formulation was changed from missing (b) (4) to 16.35 ng/mL (half the lower limit of quantification) in this NDA. However, this concentration (16.5 ng/mL) at 36 hours was used only for the computation of summary statistics. The AUC from the last sampling time to infinity was calculated after replacing the 36 hour value with missing in both the NDA's, therefore, although the concentration-time profile were different between the two NDA's, the AUC_{0-∞} estimates were identical.

2. For subject 25, the concentrations reported in this NDA (b) (4) are identical, however, the AUC estimates are different.

The sponsor acknowledged that the differences in AUC estimates were due to an error during the reanalysis of the final dataset of lamivudine plasma concentrations. This error was corrected and the pharmacokinetic parameters and bioequivalence statistics were recomputed. Tables 1 and 2 reflect the updated estimates.

3. For subjects 16, 23, and 24, the concentrations reported in this NDA (b) (4) were different, however, the AUC estimates were identical. Also, please explain the discrepancy between the concentrations for subject 16.

The sponsor provided a similar explanation as outlined under comment # 1.

FINAL RESULTS

Lamivudine Reference Formulation

Table 1 shows the pharmacokinetic parameters (computed based on untransformed data) and the test-to-reference point estimates and 90 % confidence intervals for lamivudine.

Table 1: Lamivudine Primary Pharmacokinetic Parameters (Untransformed)

Parameter	Mean (s.d)		90 % CI	Point Estimates
	Test	Reference		
C _{max} (ng/mL)	1727 (457.6)	1844 (600.3)	84.31 %-102.99 %	93.65 %
AUC _{0-∞} (ng*hr/mL)	6448. (1103.5)	6780 (1216.7)	89.93 % - 100.49 %	95.16 %

Table 2 shows the pharmacokinetic parameters (computed based on natural log transformed data) and the test-to-reference point estimates and 90 % confidence intervals for lamivudine.

Table 2: Lamivudine Primary Parameters Summary Statistics (ln-transformed data)

Parameter	Geometric Mean		90 % CI	Point Estimates
	Test	Reference		
C_{max} (ng/mL)	1671	1746	85.90 %-106.67 %	95.72 %
AUC_{0-t} (ng*hr/mL)	5983	6278	90.2 %-100.84 %	95.37 %
$AUC_{0-\infty}$ (ng*hr/mL)	6360	6679	89.87 %-101.06 %	95.30 %

Table 3 shows the pharmacokinetic parameters (computed based on untransformed data) and the test-to-reference point estimates and 90 % confidence intervals for zidovudine.

Table 3: Zidovudine Primary Parameters Summary Statistics (Untransformed data)

Parameter	Mean (s.d)		90 % CI	Point Estimates
	Test	Reference		
C_{max} (ng/mL)	2072 (878.6)	1988 (746.8)	90.32 %-118.12 %	104.22 %
$AUC_{0-\infty}$ (ng*hr/mL)	2334 (528.7)	2167 (417.1)	101.76 % - 113.71 %	107.74 %

Table 4 shows the pharmacokinetic parameters (computed based on natural log transformed data) and the test-to-reference point estimates and 90 % confidence intervals for zidovudine.

Table 4: Zidovudine Primary Parameters Summary Statistics (ln-transformed data)

Parameter	Geometric Mean		90 % CI	Point Estimates
	Test	Reference		
C_{max} (ng/mL)	1899	1841	90.30 %-117.62 %	103.06 %
AUC_{0-t} (ng*hr/mL)	2220	2073	100.91 %-113.77 %	107.15 %
$AUC_{0-\infty}$ (ng*hr/mL)	2274	2126	100.83 % - 113.58 %	107.02 %

Conclusion

A single dose of the test product, (lamivudine/zidovudine 150/300 mg fixed-dose combination, Pharmacare Ltd.) and of the reference product (Combivir[®] 150 mg/300 mg tablets, GlaxoSmith Kline, SA), administered to healthy volunteers, was bioequivalent with respect to rate and extent of absorption of both the pharmaceutical ingredients.

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

/s/

Vikram Arya
8/9/2006 10:50:15 AM
BIOPHARMACEUTICS

Kellie Reynolds
8/9/2006 03:35:33 PM
BIOPHARMACEUTICS

Initial Quality Assessment
Branch IV
Pre-Marketing Assessment Division II

OND Division: Division of Anti-Viral Products
NDA: 22-018
Applicant: Aspen Pharmacare Limited
Stamp Date: Feb 24, 2006
Proposed Trademark:
Established Name: Lamivudine-zidovudine
Dosage Form: Tablets
Route of Administration: Oral
Strength: 150mg/300mg
Indication: HIV Therapy
Reviewer: Rao Kambhampati
PAL: Stephen Miller

	YES	NO
Acceptable for filing:	☒	☐
Comments for 74-Day Letter	☐	☒ None Identified

Summary and Critical Issues

Summary

Application submitted under PEPFAR for lamivudine/zidovudine tablets as a stand-alone product. (b) (4)

Product is an uncoated oval tablet (15.5 x 7.8 mm; 750 mg), imprinted with (b) (4) on one side.

Current approach in DAVP is that (b) (4) are not recommended.

Aspen is adding (b) (4)

Stability, and release data (and brief summaries of validation reports) are provided using larger scale production (b) (4)

Comments for 74-Day Letter

1) None identified.

What is a proposed timeline for review?

Internal goal will be 4-months (June 24, 2006).

Generally, PEPFAR NDAs have Priority status (6-mo PDUFA goal)

Mixed messages received from Aspen's US agent about ability of Aspen to continue with production of [REDACTED] ^{(b) (4)} This is being clarified.

D. Comments/Recommendation:

NDA is filable (formal filing meeting not anticipated).

See previous section for some potential review issues.

Team CMC review is not necessary for this NDA, although coordination of DMF reviews between the following NDAs will be very important:

Application/Reviewer	API Sources
Aspen NDA 22-018 Rao Kambhampati	[REDACTED] (b) (4)

Stephen P. Miller, Ph.D.
Pharmaceutical Assessment Lead

See DFS
Date

Elaine Morefield, Ph.D.
Division Director

See DFS
Date

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/s/

Stephen Paul Miller
5/24/2006 09:09:57 AM
CHEMIST

IQA for [REDACTED] ^{(b) (4)} Tablets

Elaine Morefield
5/24/2006 02:20:05 PM
CHEMIST