

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022344Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

******Pre-decisional Agency Information******

Memorandum

Date: May 10, 2018

To: Monica Zeballos, Regulatory Project Manager
Division of Antiviral Products (DAVP)

From: Wendy Lubarsky, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for LAMIVUDINE and TENOFOVIR
DISOPROXIL FUMARATE tablets, for oral use

NDA: 022344

In response to DAVP consult request dated January 11, 2018, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for LAMIVUDINE and TENOFOVIR DISOPROXIL FUMARATE tablets, for oral use.

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI and PPI received by electronic mail from DAVP (Monica Zeballos) on May 4, 2018, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DAVP (Monica Zeballos) on May 4, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Wendy Lubarsky at (240) 402-7721 or wendy.lubarsky@fda.hhs.gov.

61 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

WENDY R LUBARSKY
05/10/2018

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: May 10, 2018

To: Debra Birnkrant, MD
Director
Division of Antiviral Products (DAVP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Ruth Lidoshore, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Wendy Lubarsky, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): lamivudine and tenofovir disoproxil fumarate

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 022344

Applicant: Aurobindo Pharma Limited

1 INTRODUCTION

On August 21, 2017, Aurobindo Pharma Limited re-submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 022344 for lamivudine and tenofovir disoproxil fumarate tablets for final approval. The Division of Antiviral Products (DAVP) considers the Applicant's submission to be a complete, class 2 response to the Agency's action letter for Tentative Approval, issued on January 7, 2011. The proposed indication for lamivudine and tenofovir disoproxil fumarate tablets is for use in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection (b) (4)

On February 15, 2018, the Applicant submitted a major amendment to the application; therefore, the Agency extended the goal date by three months in order to provide time for a full review of the submission.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antiviral Products (DAVP) on January 12, 2018 and January 11, 2018, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for lamivudine and tenofovir disoproxil fumarate tablets.

2 MATERIAL REVIEWED

- Draft lamivudine and tenofovir disoproxil fumarate tablets PPI received on August 21, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 4, 2018.
- Draft lamivudine and tenofovir disoproxil fumarate tablets Prescribing Information (PI) received on August 21, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 4, 2018.
- Approved CIMDUO (lamivudine and tenofovir disoproxil fumarate) tablets comparator labeling dated February 28, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

RUTH I LIDOSHORE
05/11/2018

WENDY R LUBARSKY
05/11/2018

BARBARA A FULLER
05/11/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 9, 2018
Requesting Office or Division:	Division of Antiviral Products
Application Type and Number:	NDA 22344
Product Name and Strength:	Lamivudine and Tenofovir Disoproxil Fumarate Tablets, 300 mg/300 mg
Product Type:	Multi-ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Aurobindo Pharma LTD
FDA Received Date:	August 21, 2017
OSE RCM #:	2018-953
DMEPA Safety Evaluator:	Valerie S. Wilson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF REVIEW

As part of the approval process for Lamivudine and Tenofovir Disoproxil Fumarate 300 mg/300 mg tablets, the Division of Antiviral Products (DAVP) requested that we review the substantively completed package insert (SCPI) and proposed container label for areas that may lead to medication errors.

2 REGULATORY HISTORY

NDA 22344 was reviewed under the U.S. President's Emergency Plan for AIDS Relief (PEPFAR). NDA 22344 received Tentative Approval under 21 CFR 314.105 on January 7, 2011, in combination with other antiretrovirals for the treatment of HIV-1 infection (b) (4)

On August 21, 2017, Aurobindo submitted a Request for Final Approval for NDA 22344. At that time, Aurobindo also informed the Agency that they are not planning to have a proprietary name for their product.

3 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B (N/A)
ISMP Newsletters	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 FINDINGS AND RECOMMENDATIONS

Our evaluation of the substantially complete package insert (SCPI) did not identify any areas of vulnerability that may lead to medication errors.

Table 2 below includes an identified medication error issue with the submitted container label, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Aurobindo Pharma LTD (entire table to be conveyed to Applicant)

Container Labels			
	Identified Issue	Rationale for Concern	Recommendations
1.	An area for the lot number statement and expiration date is not indicated on the container label.	The lot number statement and expiration date are required on the immediate container label per 21 CFR 201.10(i)(l) and 21 CFR 201.17, respectively.	Ensure the lot number statement and expiration date are included on the immediate container label per 21 CFR 201.10(i)(l) and 21 CFR 201.17, respectively. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend using a format for the expiration date like either: DDMMYYYY (e.g., 31JAN2013) MMYYYY (e.g., JAN2013) YYYY-MMM-DD (e.g., 2013-JAN-31) YYYY-MM-DD (e.g., 2013-01-31)

5 CONCLUSION

Our evaluation of the proposed container label identified one area of vulnerability that may lead to medication errors. Above, we have provided recommendation in Table 2 for the Applicant. We ask that the Division convey Table 2 in its entirety to the Applicant so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Lamivudine and Tenofovir Disoproxil Fumarate tablets that Aurobindo Pharma LTD submitted on August 21, 2017.

Table 3. Relevant Product Information for Lamivudine and Tenofovir Disoproxil Fumarate	
Initial Approval Date	January 7, 2011 (Tentative Approval)
Active Ingredient	Lamivudine and Tenofovir Disoproxil Fumarate
Indication	In combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection (b) (4)
Route of Administration	Oral
Dosage Form	Tablet
Strength	Lamivudine 300 mg/Tenofovir Disoproxil Fumarate 300 mg
Dose and Frequency	One tablet once daily with or without food
How Supplied	Bottles of 30 tablets
Storage	Store (b) (4)
Container Closure	Bottles with child-resistant closure

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following Lamivudine and Tenofovir Disoproxil Fumarate tablets labels and labeling submitted by Aurobindo Pharma LTD.

- Container label received on August 21, 2017
- Prescribing Information (Image not shown) received on August 21, 2017

F.2 Label and Labeling Images

(b) (4)



^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

VALERIE S WILSON
05/09/2018

OTTO L TOWNSEND
05/09/2018

MEMORANDUM

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

DATE: July 9, 2010

TO: Debra B. Birnkrant, M.D.
Director
Division of Antiviral Products (DAVP)

FROM: Michael F. Skelly, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. *Martin K. Yau 7/9/10*
Acting Team Leader (Bioequivalence)
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDA 22-344, Lamivudine and
Tenofovir Disoproxil Fumarate Tablets, sponsored by
Aurobindo Pharma Limited

At the request of the Division of Antiviral Products (DAVP), the Division of Scientific Investigations (DSI) conducted audits of clinical and analytical portions of the following bioequivalence studies:

Study #199/09: "An open label, randomized, two-treatment, two-sequence, two-period, crossover, single-dose comparative oral bioavailability study of a fixed dose combination of Lamivudine and Tenofovir disoproxil fumarate 300/300 mg tablets (Test) of Aurobindo Pharma Ltd., India and Epivir 300 mg tablets (Reference) of GlaxoSmithKline, Research Triangle Park, USA & Viread 300 mg tablets (Reference) of Gilead Sciences, Inc., USA in 36 healthy, adult, male human subjects under fasting conditions"

Study #200/09: An open label, randomized, two-treatment, two-sequence, two-period, crossover, single-dose comparative oral bioavailability study of a fixed dose combination of Lamivudine and Tenofovir disoproxil fumarate 300/300 mg tablets (Test) of Aurobindo Pharma Ltd., India and Epivir 300 mg tablets (Reference) of GlaxoSmithKline, Research

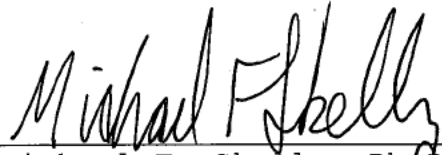
Triangle Park, USA & Viread 300 mg tablets
(Reference) of Gilead Sciences, Inc., USA in
36 healthy, adult, male human subjects under fed
conditions

The clinical portions of the studies were conducted at Trident Life Sciences Limited (now Axis Clinicals Ltd.), and the analytical portions of the studies were conducted at APL (Aurobindo Pharma Ltd.) Research Centre, both in Hyderabad, India. DSI audited the clinical portions of the studies at Axis Clinicals and the analytical portions of the studies at Aurobindo. Following the inspection at Axis (May 31-June 9, 2010), no Form FDA 483 was issued. Following the inspection at APL (June 2-June 11, 2010), Form FDA 483 was issued. DSI received a response to the Form FDA 483 observations from APL on June 24. Our evaluation of the Form FDA 483 observations and the firm's response follows:

(b) (4)



After you have reviewed this transmittal memo, please append it
to the original NDA submission.


Michael F. Skelly, Ph.D.

Final Classifications:

NAI - Axis Clinicals (formerly Trident Life Sciences),
Hyderabad, India
FEI 3006649033
VAI - APL Research Centre
Hyderabad, India
FEI 3004918125 (also designated 3007392429)

CC:

DSI/GLPBB/Yau/Rivera-Lopez/CF
OTS/OCP/DCP4/Lazor
OTS/OCP/DCP4/Noory
OTS/OCP/DCP4/Zeballos
HFR-SW4505/Iwen
OC/DSI/Ball
OC/DSI/Haidar
Draft: MFS 7/6/10
Edit: MKY 7/6/10

Page 6 - NDA 22-344, Lamivudine and Tenofovir Disoproxil
Fumarate Tablets, Sponsored by Aurobindo Pharma Limited

DSI: 6046

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FACTS: 1157514

Email:

CDER DSI PM TRACK

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22344	ORIG-1	AUROBINDO PHARMA LTD	Lamivudine/Tenofovir Dioxoproxil Fumarate FDC Tablets (300 mg/300)

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/s/

MICHAEL F SKELLY

07/13/2010

Dr. Yau signed the paper copy on 7/9/10. The original signed copy is available in the DSI file.