

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022344Orig1s000

CLINICAL REVIEW(S)

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

DATE: May 14, 2018

FROM: Jeff Murray, M.D.
Division of Antiviral Products

SUBJECT: Deputy Director Memorandum for NDA 22344
Lamivudine and Tenofovir Disoproxil Fumarate Tablets,
300mg/300mg

APPLICANT: Aurobindo Pharma LTD (Aurobindo)

TO: Division files

I. Background

Aurobindo submitted this 505(b)(2) new drug application (NDA) for Lamivudine (3TC) and Tenofovir Disoproxil Fumarate (TDF) Tablets, 300 mg/300 mg, intended for adult and pediatric patients weighing at least 35 kg. The two drugs in this fixed dose combination (FDC) are widely used in antiretroviral regimens and with the addition of a third drug make a complete regimen considered standard-of-care for a treatment naïve, HIV-1 infected patient.

This application was originally submitted on March 9, 2010 and received a Tentative Approval (TA) on Jan. 11, 2011, under PEPFAR (President's Emergency Plan for AIDS Relief). The applicant resubmitted the application on Aug. 21, 2017, for marketing approval in the U.S. with expiration of relevant patents and exclusivity that previously precluded final approval in 2010.

II. Reviewers Findings

Please refer to the Office of Pharmaceutical Quality (OPQ) reviews for details on chemistry, manufacturing and controls (CMC). For this resubmission, refer to OPQ review, resubmission 31, prepared with concurrence from the OPQ Application Team Lead, Stephen Miller, Ph.D. The OPQ reviewers recommend Aurobindo's Lamivudine and Tenofovir Disoproxil Fumarate Tablets, 300 mg/300 mg, for final approval.

Also, refer to my memorandum dated Jan. 7, 2011, summarizing the findings supporting tentative approval of this fixed dose combination. In brief, in support of tentative approval, the applicant submitted two bioequivalence studies (fasted and fed) assessing performance of their fixed dose combination product

containing lamivudine and tenofovir DF compared to the US reference listed drugs for these active ingredients, Epivir and Viread, respectively. In both studies the 90% confidence intervals for tenofovir DF and lamivudine are within 80% - 125% for both AUC and Cmax, indicating that tenofovir and lamivudine combination tablets are bioequivalent to Viread® plus Epivir®.

Refer to the labeling memorandum, prepared by Monica Zeballos Pharm.D., which summarizes updates to the label since initial TA, discusses the inclusion of pediatric age groups and summarizes pertinent regulatory issues.

III. Recommendations

I concur with the final approval of Aurobindo's Lamivudine and Tenofovir Disoproxil Fumarate FDC Tablets, 300 mg/300 mg, for the treatment of HIV-1 in combination with other antiretroviral drugs in adult and pediatric patients weighing at least 35 kg.

Jeffrey S. Murray M.D., M.P.H.
Deputy Director, Division of Antiviral Products

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/s/

JEFFREY S MURRAY
05/14/2018

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Division of Antiviral Products
Food and Drug Administration
Center for Drug Evaluation and Research
Silver Spring, MD 20993

Clinical Labeling Review

Date	May 1, 2018
From	Monica Zeballos, Pharm.D. Program Coordinator Division of Antiviral Products (DAVP)
Through	Jeffrey Murray, M.D., M.P.H., Deputy Director, DAVP
NDA #	NDA 22344
Original Regulatory Action and Date	PEPFAR, Tentative Approval (TA) on 07Jan2010
Applicant	Aurobindo Pharma Limited (Aurobindo), India
U.S. Agent	Aurobindo Pharma USA, Inc., POC: Blessy Johns
Letter Date	August 21, 2017
Stamp Date	August 21, 2017
Goal Date	May 21, 2018 (due to a major amendment extension)
Established Name	Lamivudine and Tenofovir Disoproxil Fumarate
Tradename	None
Dosage Form/Strength	Tablets, 300 mg/300 mg
Subject	Class 2 Resubmission to a TA, Requesting Final Approval
Materials Reviewed and Labeling Consultant Reviews	1. Electronic Resubmission (SDN31 in DARRTS and NDA-022018-ORIG-1-RESUB-31 in Panorama) dated and received 21Aug2017 2. Current U.S. labeling for the reference products: a) NDA 20564 EPIVIR (lamivudine) tablets, 300 mg approved on 27April2018 and b) NDA 21356 VIREAD (tenofovir disoproxil fumarate) tablets, 300 mg approved 07April2017 3. OSE/DMEPA^a Review of the PI & Container/Carton Labeling dated 09May2018 4. OMP/OPDP^b Review of the PI and Container/Carton Labeling dated 10May2018 5. Combined OMP/OPDP^b and OMP/DMPP^c Review of the PPI dated 11May2018 6. OPQ^d Labeling Recommendations for the PI/PPI & Container/Carton Labeling dated 14May2018
Recommended	Approval

^aOffice of Surveillance and Epidemiology/Division of Medication Error Prevention and Analysis

^bOffice of Medical Policy/Office of Prescription Drug Promotion (formerly DDMAC)

^cOffice of Medical Policy/Division of Medical Policy Programs (Patient Labeling Team)

^dOffice of Product Quality

I. Background

Aurobindo's original 505(b)(2) complete NDA 22344 submitted on 09March2010 was reviewed under the President's Emergency Plan for AIDS Relief (PEPFAR) and granted tentative approval (TA) on 07January2011.

On 21Aug2017, Aurobindo submitted a class 2 resubmission to a TA to gain final approval and marketing in the United States. Aurobindo requested approval: 1) following expiration on 25Jan2018 of patent/pediatric exclusivity protection associated with referenced NDA 21356 for VIREAD and 2) prior to the expiration of D-147 exclusivity associated with referenced NDA 20564 for EPIVIR expiring in 23March2018

(b) (4)

Aurobindo's proposed indication for use in combination with other antiretroviral agents for the treatment of HIV-1 infection "in adults and pediatric patients (b) (4)

(b) (4)" was revised by DAVP to "adult and pediatric patients weighing at least 35 kg."

The Office of Chief Counsel determined that the 3-year D-147 exclusivity for EPIVIR was granted in error and was removed from the Orange Book in Jan 2018. Thus, it was not necessary to consider the exclusivity implications, if any, for purposes of this approval.

(b) (4)

DAVP determined to (b) (4) use the

(b) (4) weight limit for this product.

On 15Feb2018, Aurobindo submitted a major amendment to this NDA and additional time was needed to evaluate the responses and conduct inspections for two new manufacturing facilities in the supply chain of DMF (drug master file) for lamivudine. Thus, the original 21Feb2018 resubmission goal date was extended by 3 months to 21May2018.

To date, Aurobindo has submitted six manufacturing amendments that allowed changes to this NDA after tentative approval and were internally tracked and reviewed as manufacturing supplements. OPQ has reviewed all six manufacturing amendments and issued PEPFAR Permitted letters for all of them. No labeling amendments were submitted and there are no pending or further manufacturing changes submitted for review.

II. Labeling Review

All sections of the Prescribing Information (PI) and Patient Package Insert (PPI) for this 2-drug fixed-dose combination (FDC) product were reviewed, updated, and compared to the latest approved U.S. labeling for EPIVIR and VIREAD. Labeling recommendations for the PI and PPI from consulting offices (OPQ, OSE/DMEPA, OMP/OPDP, OMP/DMPP) are included in the annotated PI and the content and format of the PPI was completely reformatted to be consistent with EPIVIR's PPI and current practices. A clean copy of the PPI and an annotated PI are attached at the end of this memo. Labeling recommendations for the container/carton labels were addressed separately.

The content and format of the proposed PI has been updated and revised. Notable revisions include:

1. Because there was no tradename for this product, the Division considers “lamivudine and tenofovir disoproxil fumarate tablets” the drug product in singular vs. the plural tablets, thus “is” was used throughout the PI/PPI when referring to the drug product. In addition, in this case, the Division prefers adding the word “tablets” as part of the drug product name because leaving it out creates ambiguity for some sentences.
2. Revised the proposed INDICATION AND USAGE section as follows:

Lamivudine and tenofovir disoproxil fumarate tablets is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adult and pediatric patients weighing at least 35 kg.

3. Addition to DOSAGE AND ADMINISTRATION:

2.1 Testing Prior to Initiation and During Treatment with Lamivudine and Tenofovir Disoproxil Fumarate Tablets

Prior to initiation of lamivudine and tenofovir disoproxil fumarate tablets, test patients for hepatitis B virus infection [see *Warnings and Precautions* (5.2)].

It is recommended that serum creatinine, serum phosphorus, estimated creatinine clearance, urine glucose, and urine protein be assessed before initiating lamivudine and tenofovir disoproxil fumarate tablets and during therapy in all patients as clinically appropriate [see *Warnings and Precautions* (5.5)].

2.2 Recommended Dosage for Adult and Pediatric Patients Weighing at Least 35 kg

Lamivudine and tenofovir disoproxil fumarate tablets is a two-drug fixed-dose combination product containing 300 mg of lamivudine (3TC) and 300 mg of tenofovir disoproxil fumarate (TDF). The recommended dosage of lamivudine and tenofovir disoproxil fumarate tablets in HIV-1-infected adult and pediatric patients weighing at least 35 kg is one tablet taken orally once daily with or without food.

4. Important information for the individual components (EPIVIR and VIREAD) relevant to the use of this combination product was added to the WARNINGS AND PRECAUTIONS (5), ADVERSE REACTIONS (6), DRUG INTERACTIONS (7), USE IN SPECIFIC POPULATIONS (8), CLINICAL PHARMACOLOGY (12), HOW SUPPLIED/STORAGE AND HANDLING, and PATIENT COUNSELING INFORMATION (17) sections as follows:
 - Section 5: Added updated information regarding New Onset or Worsening Renal Impairment and Bone Effects for TDF
 - Section 6.1: Added adverse reactions information supported by clinical trial 903 in treatment-naïve in adults that covers both lamivudine and TDF tenofovir DF and bone mineral density for TDF
 - Section 7: Added lamivudine information about Drug Inhibiting Organic Cation Transporters and Sorbitol and tenofovir DF information about Hepatitis C Antiviral Agents
 - Subsections 8.4: Added pediatric use language

- Subsection 12.3: Added summarized pharmacokinetics information in adults for both lamivudine and TDF, added specific populations information for renal impairment for both lamivudine and TDF, and drug interaction information for lamivudine
- Section 16: Per OPQ's recommendations, changed storage statement based on demonstrated stability, added detailed packaging information, and storage information
- Section 17: Reformatted and added information on New Onset or Worsening Renal Impairment, Decrease in Bone Density, Pregnancy Registry, and Storage

III. Recommended Regulatory Action

The proposed PI and PPI were reviewed and should allow for the safe and effective use of this 2-drug fixed-dose combination product. Aurobindo has adequately responded to the Division's labeling revisions conveyed on May 9 and 10, 2018, via email correspondence; therefore, an approval action is warranted.

Monica Zeballos, Pharm.D.
Program Coordinator
Division of Antiviral Products
Office of Antimicrobial Products

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

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/s/

MONICA I ZEBALLOS
05/14/2018

JEFFREY S MURRAY
05/14/2018

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

DATE: January 7, 2011

FROM: Jeff Murray, M.D.
Division of Antiviral Products

SUBJECT: Deputy Director Memorandum for NDA 22-344
Lamivudine and Tenofovir Tablets 300/300mg

TO: Division files

I. Background

The availability of a wide range of safe and effective antiretroviral drug products is hoped to facilitate a wider distribution of anti-HIV drugs to better meet the demands of the global HIV/AIDS pandemic. On Oct. 17, 2006 FDA published a guidance entitled "Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV." The guidance encourages sponsors to develop various drug product versions of previously approved antiretroviral drugs and encourages sponsors to submit drug applications for these products to FDA for review. Although many antiretroviral drug product versions of previously approved antiretrovirals cannot be currently marketed in the US because of patent and exclusivity restrictions, FDA is able to review these products for quality, safety and efficacy and potentially grant a tentative approval. The President's Emergency Plan for AIDS Relief will consider procurement of products reviewed by FDA that have been granted approval or tentative approval. Such products may be distributed outside the US, depending on legal requirements in other countries.

II. Reviewers Findings

Aurobindo Pharma submitted this 505 (b)2 NDA for Lamivudine and Tenofovir Tablets (300mg/300 mg) [REDACTED] (b) (4)

[REDACTED] The two drugs in this fixed dose combination are widely used in antiretroviral regimens and with the addition of a third drug would make a complete regimen considered standard-of-care for a treatment naïve, HIV-1 infected patient (see appendix B of the aforementioned guidance).

Please refer to the Office of New Drug Quality review prepared by Brian Rogers which states, "From the CMC standpoint, the NDA# 022344 is recommended for tentative approval. Deficiencies have been resolved pertaining to drug substance

and drug product, specifications, stability protocol, and quality of stability data. Manufacturing facilities have been determined to be acceptable.”

Also refer to the Clinical Pharmacology memo prepared by Dr. Assadollah Noory, who recommends tentative approval. In support of tentative approval, the applicant submitted two bioequivalence studies (fasted and fed) assessing performance of their fixed dose combination product containing lamivudine and tenofovir compared to the US reference listed drugs for these active ingredients, Epivir and Viread, respectively. In both studies the 90% confidence intervals for tenofovir and lamivudine are within 80% - 125% for both AUC and Cmax, indicating that tenofovir and lamivudine combination tablets are bioequivalent to Viread® plus Epivir®. DSI inspection of sites revealed deficiencies, but reanalysis of data excluding subject data that may have been affected showed that exposures were still within an acceptable range.

Please refer to Dr.Moinca Zeballos’s labeling review of this application for a description of the labeling.

III. Recommendations

Lamivudine and Tenofovir Tablets (300mg/300mg) (b) (4)
should
receive tentative approval.

Jeffrey S. Murray M.D., M.P.H.

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/s/

JEFFREY S MURRAY
01/07/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Division of Antiviral Products
Food and Drug Administration
Center for Drug Evaluation and Research
Silver Spring, MD 20993

DATE: January 6, 2011

TO: NDA 22-344
Lamivudine and Tenofovir disoproxil fumarate Tablets, 300 mg/300 mg

FROM: Monica Zeballos, Pharm.D.
Senior Program Consultant
Division of Antiviral Products (DAVP)

THROUGH: Jeffrey Murray, M.D., M.P.H., Deputy Director, DAVP

SUBJECT: Clinical Labeling Review

I. Background

The purpose of this submission is to gain tentative approval of Aurobindo Pharma Limited's registration application for the following drug product:

- Lamivudine and Tenofovir disoproxil fumarate Tablets, 300 mg/300 mg

Use of simplified anti-HIV regimens in the form of co-packaged drugs (such as blister packs) or fixed-dose combinations (FDCs) may facilitate distribution and improve patient adherence in the United States and developing countries. To facilitate more rapid development of FDCs or co-packaging of antiretroviral agents, FDA issued a Guidance for Industry on *Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV* (October 2006). This guidance is intended to encourage applicants to submit applications to the FDA for approval of FDCs and co-packaged versions of previously approved antiretroviral therapies.

Aurobindo Pharma Limited's application was submitted in response to this guidance as a 505(b)(2) application for this product containing two widely used antiretroviral drugs, lamivudine and tenofovir disoproxil fumarate. The safety and efficacy of these products is supported by previously conducted adequate and controlled studies of the approved components: Epivir (lamivudine) and Viread (tenofovir disoproxil fumarate), also called reference listed drugs (RLDs). Because the RLDs for this product are under patents, the application cannot be approved but is eligible to receive tentative approval which recognizes that, at the time the tentative approval action is taken, the application meets the regulatory and scientific requirements for approval, but final approval is blocked by patents or exclusivities. The President's Emergency Plan for AIDS Relief (PEPFAR) will consider procurement of products reviewed by FDA that have been granted approval or

tentative approval. Such products may be distributed outside the United States, depending on regulatory requirements in other countries.

II. Labeling Review

The proposed labeling in PLR (Physician's Labeling Rule) format for this fixed-dose combination product was reviewed and compared to the latest approved U.S. labeling for: Epivir® (lamivudine) tablets, approved version in PLR format 01Feb 2008 and Viread (tenofovir disoproxil fumarate) tablets, approved version in PLR format 14Oct2010. The PLR labeling for Truvada (emtricitabine and tenofovir disoproxil fumarate) tablets approved on 06Nov2009 was also used for formatting purposes.

The content of the proposed labeling for Aurobindo Pharma Limited's fixed-dose combination formulation is consistent with the U.S. labeling for Epivir and Viread. Notable differences include:

1. Because dose reductions are necessary but not possible with Lamivudine and Tenofovir disoproxil fumarate Tablets, this fixed-dose combination formulation is not indicated for use in adult and pediatric patients with impaired renal function (creatinine clearance < 50 mL/min) or patients with end-stage renal disease (ESRD) requiring hemodialysis.
2.  (b) (4)
3. The rate and extent of absorption of Lamivudine and Tenofovir DF Tablets was assessed in two studies, fasting and fed; therefore, this formulation can be taken under fasting or fed conditions.
4. Important information for the individual components relevant to the use of this combination formulation was added to WARNINGS AND PRECAUTIONS (5), ADVERSE REACTIONS (6), DRUG INTERACTIONS (7), and CLINICAL PHARMACOLOGY (12) sections as follows:
 - Section 5: Added information regarding Patients Coinfected with HIV-1 and HBV and Early Virologic Failure
 - Section 6: Added adverse reactions information supported by clinical trials in adults and pediatric patients for lamivudine and tenofovir DF
 - Section 7: Added lamivudine information regarding Interferon- and Ribavirin-Based Regimens, TMP/SMX, and Drugs with No Observed Interactions with Lamivudine and tenofovir DF information regarding Drugs Affecting Renal Function
 - Section 12.3: Added lamivudine and tenofovir DF pharmacokinetics information in adults patients and lamivudine pharmacokinetics information in pediatric patients
 - Section 12.4: Added lamivudine and tenofovir DF resistance and cross resistance information

All the sections of the package insert (PI) and patient information were reviewed and the content and format of the patient information was completely changed to be consistent with Viread's patient information.

III. Recommended Regulatory Action

The original PI was submitted in PLR format. Both the revised PI and patient information were reviewed and should allow for the safe and effective use of this fixed-dose combination formulation. The applicant has adequately responded to the Division's labeling revisions conveyed on January 6, 2011, via email correspondence; therefore, a tentative approval action is warranted.

The labeling for this double fixed-dose combination formulation is consistent with the U.S. labeling for Epivir and Viread. Dose reductions or adjustments are not possible with this formulation (b) (4)

Therefore, Lamivudine and Tenofovir DF Tablets should not be used in the following patient populations:

1. (b) (4)
2. Patients with impaired renal function (creatinine clearance < 50 mL/min) or patients with end-stage renal disease (ESRD) requiring hemodialysis

Additionally, the rate and extent of absorption of Lamivudine and Tenofovir DF Tablets was assessed in two pharmacokinetic studies under fasting and fed conditions; therefore, the recommended administration is "take with or without food" or under fasting and fed conditions.

Monica Zeballos, Pharm.D.
Senior Program Consultant
Division of Antiviral Products
Office of Antimicrobial Products

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/s/

MONICA I ZEBALLOS
01/06/2011

JEFFREY S MURRAY
01/06/2011