CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022343Orig1s000

OTHER REVIEW(S)

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

CSO Labeling Review

Date	**August 1, 2018**
From	**David Araojo, Pharm.D.** **Program Coordinator** **Division of Antiviral Products (DAVP)**
Through	**Jeffrey Murray, M.D., M.P.H., Deputy Director, DAVP**
NDA # **Supplement #**	**NDA 22343, resubmission received February 16, 2018**
Original Regulatory Action and Date	**PEPFAR, Tentative Approval (TA) on June 26, 2013**
Applicant	**Aurobindo Pharma Limited, India**
U.S. Agent	**Blessy Johns, Aurobindo Pharma USA, Inc.**
Letter Date	**February 15, 2018**
Stamp Date	**February 16, 2018**
PDUFA Goal Date	**August 16, 2018**
Established Name	**Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate**
Proprietary Name	**n/a**
Dosage Form/Strength	**Tablets, 600 mg/300 mg/300 mg**
Subject	**Class 2 Resubmission to a TA, Requesting Final Approval**
Materials Reviewed	➢ **Electronic Resubmission dated February 15, 2018** ➢ **Current U.S. labeling for SUSTIVA (efavirenz), EPIVIR (lamivudine) and VIREAD (tenofovir disoproxil fumarate)** ➢ **OSE/DMEPA Review of the PI & Container/Carton Labels** ➢ **OMP/OPDP Review of the PI, PPI & Container/Carton Labels** ➢ **OPQ Labeling Recommendations for the PI** ➢ **DPMH Review**
Recommended	**Approval**

I. Background

Aurobindo Pharma Limited's (Aurobindo) original 505(b)(2) NDA 22343 for Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate Tablets, 600 mg/300 mg/300 mg, was reviewed under the President's Emergency Plan for AIDS Relief (PEPFAR) and granted tentative approval on June 26, 2013.

Aurobindo submitted a class 2 resubmission, dated February 15, 2018, requesting final approval and marketing in the United States. The applicant requests approval and will not market in the U.S. prior to the August 14, 2018 expiration of the final applicable referenced Sustiva patent (NDA 21360). There are no unexpired patents or exclusivity for referenced NDA 21356 for Viread Tablets and NDA 20564 for Epivir Tablets.

II. Labeling Review

All sections of the Prescribing Information (PI) for this triple fixed-dose combination (FDC) product were reviewed, updated, and compared to the latest approved U.S. labeling for Sustiva Tablets, Epivir Tablets, and Viread Tablets. Labeling recommendations for the PI, Patient Package Insert (PPI), and container labels from the Office of Product Quality (OPQ), Division of Pediatric and Maternal Health (DPMH), Office of Surveillance and Epidemiology's Division of Medication Error Prevention and Analysis (DMEPA), Office of Medical Policy Initiatives (OMPI) and Office of Prescription Drug Promotion (OPDP) are included in the revised PI, PPI and container/carton labels.

Aurobindo did not submit a proprietary name for this drug product.

Please refer to the following related reviews for NDA 22343:

- OPQ, dated July 31, 2018
- DPMH, dated July 2, 2018
- DMEPA, dated June 27, 2018
- OMPI, dated June 14, 2018
- OPDP, dated June 14, 2018

The content and format of the proposed PI and PPI have been updated and revised. Please see enclosure for FDA proposed PI and PPI edits. Notable revisions include:

1. HIGHLIGHTS and FPI section:
   Indication revised to "Indicated as a complete regimen for the treatment of HIV-1 infection in adult and pediatric patients weighing at least 40 kg."

2. Addition to DOSAGE AND ADMINISTRATION:
   2.1 Testing Prior to Initiation and During Treatment with Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets
   Prior to initiation of Efavirenz, 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 Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets and during therapy in all patients as clinically appropriate [see Warnings and Precautions (5.5)].
   Monitor hepatic function prior to and during treatment with Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets [see Warnings and Precautions (5.9)].

3. Addition to CONTRAINDICATIONS:
   Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets is contraindicated
   • in patients with a previous hypersensitivity reaction (e.g., Steven-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components contained in the formulation [see Warnings and Precautions (5.9)].
   • when coadministered with elbasvir and grazoprevir [see Warnings and Precautions (5.3) and Drug Interactions (7.4)].

4. Addition to WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS, respectively:

5.1 Lactic Acidosis and Severe Hepatomegaly with Steatosis
A majority of these cases have been in women. Female sex and obesity may be risk factors for the development of lactic acidosis and severe hepatomegaly with steatosis in patients treated with antiretroviral nucleoside analogues.

5.11 Pancreatitis
In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, 3TC, a component of Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, should be used with caution. Treatment with Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur [see Adverse Reactions (6.1)].

And:
Pancreatitis: Pancreatitis, which has been fatal in some cases, has been observed in antiretroviral nucleoside-experienced pediatric subjects receiving 3TC alone or in combination with other antiretroviral agents *[see Warnings and Precautions (5.11)].*

5. Addition in DRUG INTERACTIONS:
    - Updated Table 5 to add new Hepatitis C antiviral agent drug interactions, similar update in Section 12.3 Pharmacokinetics
    - Addition of drugs inhibiting organic cation transporters
    - Addition of sorbitol drug interaction

6. Revised USE IN SPECIFIC POPULATIONS:
   Information related to efavirenz and lamivudine were updated to conform with the Pregnancy and Lactation Labeling Rule.

   Section 8.4 Pediatric Use updated to:
   The safety and effectiveness of Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets as a fixed dose tablet in pediatric patients infected with HIV-1 and weighing at least 40 kg have been established based on clinical studies using the individual components (efavirenz, lamivudine, and tenofovir disoproxil fumarate).

III. Recommended Regulatory Action

The proposed PI and PPI were reviewed and should allow for the safe and effective use of this fixed-dose combination product. Aurobindo has adequately responded to the Division's labeling revisions via official submission dated July 27, 2018 and email concurrence on August 9, 2018; therefore, an approval action is warranted.

_____
David Araojo, Pharm.D.
Program Coordinator
Division of Antiviral Products
Office of Antimicrobial Products

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DAVID E ARAOJO
08/10/2018

JEFFREY S MURRAY
08/10/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs/Office of Drug Evaluation IV Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Pediatric Labeling Review

From:	Carolyn L. Yancey, MD, Medical Officer Division of Pediatric and Maternal Health (DPMH)
Through:	Hari Cheryl Sachs, MD, Pediatric Team Leader DPMH John J. Alexander, MD, MPH, Deputy Director DPMH
NDA Number:	22343
Sponsor:	Aurobindo Pharma USA, Inc.
Drug:	Efavirenz (EFV), Lamivudine (3TC), Tenofovir Disoproxil Fumarate (TDF) Tablets
Therapeutic Class:	Antiretroviral combination products
Dosage Form and Route of Administration:	Fixed-dose of EFV/3TC/TDF (600 mg, 300 mg, 300 mg) oral tablet
Reference Products:	Sustiva (EFV) Tablets 600 mg, NDA 021360, Bristol-Myers Squibb Company Epivir (3TC) Tablets 300 mg, NDA 020564, ViiV Healthcare Company Viread (TDF) Tablets 300 mg, NDA 021356, Gilead Sciences, Inc.
Approved Indications:	**Sustiva:** In combination with other antiretroviral agents for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and in pediatric patients at least 3 months old and weighing at least 3.5 kilogram (kg). **Epivir:** In combination with other antiretroviral agents for the treatment of HIV-1 infection. [Section 2. Dosage and Administration: (2.2)

Pediatric patients aged 3 months and older, recommended dosing is [redacted] orally twice daily or [redacted] orally once daily (up to a maximum of 300 mg daily)]. Epivir scored tablet is preferred in pediatric patients weighing at least 14 kg and for whom a tablet is appropriate.

Viread:
In combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and in pediatric patients 2 years of age and older. [Tablet is available for pediatric patients weighing at least 17 kg and who can swallow a tablet. One tablet (150, 200, 250, or 300 mg/day based on body weight), once daily.]

Proposed Indication: Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets is a three-drug combination of efavirenz (EFV), a non-nucleoside reverse transcriptase inhibitor, and lamivudine (3TC) and tenofovir disoproxil fumarate (TDF), both nucleo(t)side reverse transcriptase inhibitors and is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adult and pediatric patients weighing at least 40 kg.

Consult Request: The Division of Antiviral Products (DAVP) requests DPMH's input on proposed labeling for the 505(b)(2), class 2 resubmission for new drug application (NDA) [redacted] for EFV/3TC/TDF (600 mg/300 mg/300 mg) fixed-dose combination (FDC), oral tablet by Aurobindo Pharma USA, Inc. (consult dated April 24, 2018). NDA 22343 received a tentative approval (TA) on June 26, 2013 under the Code of Federal Regulations (CFR) 314.105. This NDA was originally submitted under the expedited review provisions of the President's Emergency Plan for AIDS Relief (PEPFAR)[1] which means that although it has TA, it can be procured with PEPFAR funds to be actively distributed outside of the United States (US). On February 16, 2018, Aurobindo Pharma USA, Inc. submitted a class 2 resubmission application requesting final approval for US marketing. DAVP requests assistance in determining whether any protected pediatric information should be retained or added, and whether a disclaimer statement is appropriate in labeling.

Background:
The labeling under review is for the fixed dose combination (FDC) of three approved antiretroviral drug products, EFV/3TC/TDF (600 mg, 300 mg, 300 mg), under 505(b)(2), NDA 22343, manufactured by Aurobindo Pharma USA, Inc. On June 26, 2013, DAVP granted NDA 22343 TA under PEPFAR.[2] On February 16, 2018, the applicant submitted a class 2 resubmission application

[1] PEPFAR enacted in 2003 by Congress supports treatment of infectious diseases (HIV-AIDS pandemic) in underserved countries across the world to decrease AIDS. Under PEPFAR provisions, a product can be procured with PEPFAR funds for distribution outside of the United States. PEPFAR is managed by the U.S. Department of State's Office of US Global AIDS Coordinator and Health Diplomacy. See www.PEPFAR.gov

[2] [redacted]

seeking full approval of NDA 22343 for FDC product, EFV/3TC/TDF (600 mg/300 mg/300 mg) oral tablet. This proposed FDC product has been fully assessed for pediatric patients weighing at least 40 kilograms (kg).

The initial pediatric study plan (iPSP) for NDA 22343 FDC product with the same three drug components (EFV, 3TC, and TDF) was discussed at the Pediatric Review Committee (PeRC) on July 12, 2017 and PeRC concurred with a plan for a partial waiver for pediatric patients weighing less than 40 kg because the product fails to represent a meaningful therapeutic benefit over existing therapies. Therefore, pediatric assessments on pediatric patients weighing more than 40 kg were required to be submitted for the planned 505(b)(2), NDA 22343. However, all PREA study requirements and written request (WR), where applicable, for each individual component of this FDC product have been fulfilled. As cited above, this FDC product has been fully assessed for pediatric patients weighing at least 40 kg.

Reviewer Comments: Symfi (NDA 022142) contains the same drug components efavirenz, lamivudine, and tenofovir disoproxil fumarate (600 mg, 300 mg, 300 mg) and is approved for the same indication and dosing regimen. Therefore, approval of EFV, 3TC, TDF (600 mg, 300 mg, 300 mg) does not prompt requirements under PREA for NDA 22343 and can be labeled for pediatric patients weighting at least 40 kg.

Reference Drug Products

- Sustiva (efavirenz) Tablet, NDA 021360 by Bristol-Myers Squibb
- Epivir (lamivudine) Tablet, NDA 020564 by ViiV Healthcare
- Viread (tenofovir disoproxil fumarate) Tablet, NDA 021356 by Gilead Sciences, Inc.

Regulatory History Summary

See the previous DPMH review[3] for a detailed regulatory history of each individual component of the FDC product, SYMFI-LO (400 mg, 300 mg, 300 mg) and SYMFI (600 mg, 300 mg, 300 mg). Aurobindo Pharm USA, Inc. agrees to not market the FDC product under NDA 22343 [EFV, 3TC, TDF (600 mg, 300 mg, 300 mg)] until expiration of the remaining use patent on August 14, 2018.[4]

DPMH Pediatric Labeling Recommendations

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57 (c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population.

DPMH concludes that this FDC product is appropriate for pediatric patients weighing at least 40 kg and who can swallow an oral tablet based on the strength of the individual ingredients in this proposed FDC product. Sustiva (EFV), is the drug component that establishes the limit on weight-based dosing. A patient needs to weigh at least 40 kg to be administered an EFV daily dosage of 600 mg. Epivir (3TC), a scored tablet (maximum dose up to 300-mg once daily), is labeled as the preferred formulation for pediatric patients who weigh at least 14 kg and who can swallow a tablet. Viread (TDF) is labeled for pediatric patients 12 years and older weighing at least 35 kg to be administered a dosage of 300 mg once daily (see the **Appendix**, in this review, **Tables 1** thru **3,** Pediatric Dosing Recommendations).

[3] NDA 208255 Symfi Lo (efavirenz, lamivudine and tenofovir disoproxil fumarate) 600-mg, 300-mg, 300-mg Tablets, written by Carolyn L. Yancey, MD (dated February 2, 2018).

[4] See letter to DAVP from Aurobindo Pharma USA, Inc., entitled, Request for Final Approval, received by DAVP on February 15, 2018.

As cited earlier, there is no protected pediatric information and this FDC product is fully assessed for pediatric patients weighing at least 40 kg as included labeling, pediatric use information. DPMH agrees that a weight limitation (of at least 40 kg body weight) included in the following sections of labeling: Section 1. Indications and Usage, Section 2. Dosage and Administration, and Section 8. Use in Specific Populations, subsection 8.4 Pediatric Use for pediatric patients with HIV-1 infection.

DPMH recommended information to be added to labeling is underlined. Information to be deleted has a ~~strikethrough~~. Comments and rationale for DPMH's recommendations to the labeling revisions are in *italics.*

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets is a three-drug combination of efavirenz (EFV), a non-nucleoside reverse transcriptase inhibitor, and lamivudine (3TC) and tenofovir disoproxil fumarate (TDF), both nucleo(t)side reverse transcriptase inhibitors and is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adult and pediatric patients weighing at least 40 kilograms.

Reviewer's Comment:
DPMH agrees with the above language in Indications and Usage citing that this FDC tablet is only appropriate for pediatric patients weighing at least 40 kg, as detailed earlier in this review.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets are indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adult and pediatric patients weighing at least 40 kilograms.

Reviewer's Comment: DPMH agrees with the above language in Indications and Usage.

2 DOSAGE AND ADMINISTRATION

2.2 Recommended Dosage for Adult and Pediatric Patients Weighing at least 40 kilograms

Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets are a three-drug fixed-dose combination product containing 600 mg of efavirenz (EFV), 300 mg of lamivudine (3TC), and 300 mg of tenofovir disoproxil fumarate (TDF). The recommended dosage of Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets in HIV-1-infected adults and pediatric patients who weigh at least 40 kg, and can swallow a solid tablet, is one tablet taken orally once daily. Efavirenz, Lamivudine and Tenofovir Fumarate Tablets (b) (4) -should be taken on an empty stomach, preferably at bedtime. Dosing at bedtime may improve the tolerability of nervous system symptoms *[see Warnings and Precautions (5.6) and Adverse Reactions (6.1)]*.

Reviewer's Comment: DPMH agrees with the above language (with one strikethrough on the (b) (4) *) that addresses dosage and administration in pediatric patients weighing at least 40 kg.*

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets as a fixed dose tablet in pediatric patients infected with HIV-1 and weighing at least 40 kg have been established based on clinical studies using the individual components (efavirenz, lamivudine, and tenofovir disoproxil fumarate).

Reviewer's Comments:
DPMH agrees with the above information based on clinical studies using the approved individual FDC tablet components (efavirenz, lamivudine, and tenofovir disoproxil fumarate) in pediatric patients with HIV-1 and weighing at least 40 kg.

17 PATIENT COUNSELING INFORMATION

Patient Information
Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets

What is Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets?

Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets is a prescription medicine that is used without other anti(b) (4)viral medicines to treat Human Immunodeficiency Virus-1 (HIV-1) in adults and children weighing at least 88 pounds (40 kg).

HIV-1 is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets contains the prescription medicines efavirenz, lamivudine and tenofovir disoproxil fumarate.

Reviewer Comment: DPMH agrees with the above information on efavirenz, lamivudine and tenofovir disoproxil fumarate tablets in this subsection of Patient Information.

General Comments

DPMH reviewed the applicant's proposed labeling for Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate (600 mg, 300 mg, 300 mg) Tablet, a 505(b)(2) submission under NDA 22343 by Aurobindo Pharma USA, Inc., and provided labeling recommendations in track changes for DAVP to revise the labeling to conform to the *Guidance for industry and Review Staff on Pediatric Labeling*[5]. DPMH's input will be reflected in the final labeling and the approval letter from DAVP. Labeling negotiations are ongoing. Final labeling, which will be negotiated with Aurobindo Pharma USA, Inc., may differ from the recommendations in this DPMH labeling review.

[5] www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm341394.pdf

APPENDIX:

See the individual product labeling from Section 2. Dosage and Administration, as applies to pediatric patients. Note: Highlighted patient weight and recommended dose regimen and strength support proposed labeling for the FDC product of Efavirenz, Lamivudine, Tenofovir Disoproxil Fumarate (600 mg, 300 mg, 300- mg) Tablet.

Efavirenz

Subsection 2.3 Pediatric Patients

Table 1. Efavirenz Dosing in Pediatric Patients

Patient Body Weight	Efavirenz Daily Dose	Number of Capsule or Tablets and Strength to Administer
3.5 kg to < 5 kg	100 mg	Two 50 mg capsules
5 kg to < 7.5 kg	150 mg	Three 50 mg capsules
7.5 kg to < 15 kg	200 mg	One 200 mg capsule
15 kg to < 20 kg	250 mg	One 200mg capsule + one 50 mg capsule
20 kg to < 25 kg	300 mg	One 200 mg, two 50 mg capsules
25 kg to less than 32.5 kg	350 mg	One 200 mg + three 50 mg capsules
32.5 kg to < 40 kg	400 mg	Two 200 mg capsules
At least 40 kg	600 mg	One 600 mg capsule OR three 200mg capsules
Ref: Efavirenz labeling, Section 2.3, Table 1. (approved April 2018)		

Lamivudine

Subsection 2.2 Recommended Dosage for Pediatric Patients

Table 2. (b) (4) Pediatric Patients

Weight (kg)	Once-Daily Regimen	Twice-Daily Dosing Regimen Using Scored 150-mg Tablet		
		AM Dose	PM Dose	Total Daily Dose
14 to < 20	1 tablet (150 mg)	½ tablet (75 mg)	½ tablet (75 mg)	150 mg
≥ 20 to < 25	1 ½ tablets (225 mg)	½ tablet (75 mg)	1 tablet (150 mg)	225 mg
≥ 25	2 tablets (300 mg)	1 tablet (150 mg)	1 tablet (150 mg)	300 mg
Ref: Lamivudine labeling, Section 2.2, Table 1. (approved July 2016).				

Tenofovir Disoproxil Fumarate

Subsection 2.1 Recommended Doses in Adults and Pediatric Patients 12 Years of Age and Older (35 kg or more)

Table 3. Dosing Recommendations for Pediatric Patients ≥ 2 Years of Age and Weighing ≥ 17 kg Using Tenofovir Disoproxil Fumarate Tablets

Body Weight kg	Tablets Once Daily
17 to < 22	150 mg
22 to < 28	200 mg
28 to < 35	250 mg
≥ 35	300 mg
Ref: Tenofovir Disoproxil Fumarate labeling, Section 2.2, Table 1. (approved April 2017)	

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/s/

CAROLYN L YANCEY
07/02/2018

HARI C SACHS
07/02/2018
I agree with these recommendations.

JOHN J ALEXANDER
07/02/2018

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:	June 27, 2018
Requesting Office or Division:	Division of Antiviral Products (DAVP)
Application Type and Number:	NDA 22343
Product Name and Strength:	Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate Tablets, 600 mg/300 mg/300 mg
Product Type:	Multi-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Aurobindo Pharma Limited
FDA Received Date:	February 16, 2018
OSE RCM #:	2018-386
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 Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate tablets, 600 mg/300 mg/300 mg, the Division of Antiviral Products (DAVP) requested that we review the proposed label and labeling for areas that may lead to medication errors.

2 REGULATORY HISTORY

NDA 22343 was reviewed under the U.S. President's Emergency Plan for AIDS Relief (PEPFAR). On June 26, 2013, NDA 22343 received Tentative Approval under 21 CFR 314.105 for use of Efavirenz, Lamivudine, Tenofovir Disoproxil Fumarate (b) (4) for the treatment of HIV-1 infection in adults and (b) (4) weighing at least 40 kg.

On February 16, 2018 Aurobindo submitted a Request for Final Approval to NDA 22343. 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)
Response to March 8, 2018 Information Request	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

Tables 2 and 3 below include identified medication error issues with the submitted label and labeling for Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate tablets, DMEPA's rationale for concern, and proposed recommendations to minimize the risk for medication errors.

Table 2: Identified Issues and Recommendations for Division of Antiviral Products

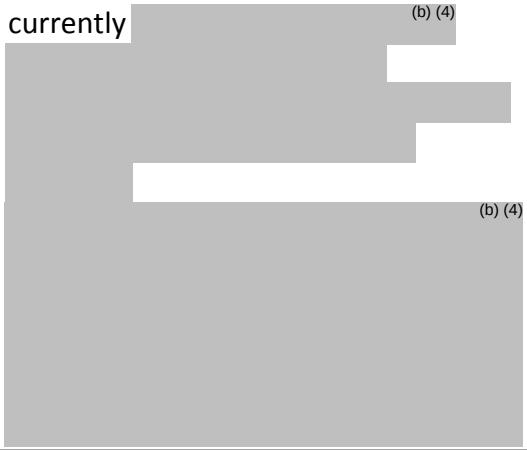
Prescribing Information			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Highlights of Prescribing Information (HPI)			
1.	Hepatic impairment dosage information is not included under the Dosage and Administration section.	The Warnings and Precautions and Use in Specific Populations sections of the Full Prescribing Information describe hepatotoxicity risk with efavirenz, one component of this fixed-dose combination tablet, stating it is not recommended for use in patients with moderate to severe hepatic impairment. We are concerned that Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate Tablets may be inadvertently used in individuals with moderate to severe hepatic impairment because this information may be missed as it is not readily available in the HPI.	To mitigate overlooking important dosing information pertaining to hepatic impairment, consider including a statement of use in individuals with hepatic impairment under the Dosage and Administration section of the HPI.
Full Prescribing Information (FPI)			
2.	In section 2.1, the recommended dose is stated as "one tablet (b) (4) Additionally, we note inclusion of (b) (4)	The use of (b) (4) does not clearly define the once daily dosing frequency at which Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate tablets are to be taken. The statement, (b) (4)	To provide clarity, consider revising the recommended dosage statement to state the frequency as once daily and remove (b) (4) from the recommended

	[redacted] within the recommended dosage statement.	[redacted] distracts from the dosing information.	dosage statements in Section 2 and the Highlights of Prescribing Information. We recommend the statement be revised to read, for example, *"The recommended dose of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate tablets is one tablet once daily taken on an empty stomach, preferably at bedtime."*
3.	The title of Section 2.2, [redacted] is misleading.	The title of section 2.2 may cause confusion because it is not indicative of the information provided in that section. Section 2.2 states [redacted] is not recommended for [redacted] patients with impaired renal function. The fixed-dose combination tablet dosage form does not facilitate ease of dose adjustment in renal impairment. For example, it is not possible to renally adjust the dose of one component, lamivudine, (i.e. decrease the dose) without affecting the dose of the other two components of this tablet.	To provide clarity, consider retitling Section 2.2 to *Not Recommended in Renal Impairment*.
4.	Section 2 does not include dosage information pertaining to use of Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate	We are concerned that Efavirenz, Lamivudine, and Tenofovir Disoproxil Tablets may be inadvertently used in individuals with moderate to severe hepatic impairment because the	To mitigate overlooking dosing recommendations for individuals with hepatic impairment, consider including a new subsection, titled for example, *Not Recommended in Moderate to Severe*

	tablets in patients with hepatic impairment.	information is not readily available under Section 2.	*Hepatic Impairment*, under Section 2 to convey to prescribers that the use of Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate Tablets is not recommended in patients with moderate to severe hepatic impairment.
5.	A description of the Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate tablet is not included in Sections 3 and 16.	Appropriate information to facilitate identification of the dosage form is required per 21 CFR 201.57(c)(4)(ii) and 21 CFR 201.57(c)(17)(iii). We are concerned that omission of this information will prevent ease of identifying Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate tablets.	To facilitate identification of the dosage form, we recommend including appropriate tablet description information, such as shape, color, coating, and imprinting in Sections 3 and 16 per 21 CFR 201.57 (c)(4)(ii) and 21 CFR 201.57(c)(17)(iii), respectively.
6.	In Section 16, the storage statement does not include the equivalent Fahrenheit temperature, which could lead to confusion and storage errors.	Fahrenheit temperature is used and understood more by end users in the US.	To mitigate storage errors, we recommend revising the storage statement to read: *Store below 30°C (86°F).*
7.	Section 16 includes packaging configurations for (b) (4) count bottles that are not intended to be marketed.	On March 9, 2018, in response to an Information Request, Aurobindo informed the Agency that they have no plan to commercialize (b) (4) -count bottles as the demand is only for 30-count, 90-count, (b) (4) bottles.	To provide clarity, consider removing the (b) (4) -count packaging configuration information from Section 16.
8.	Section 17 does not include administration instructions, nor does it include instruction advising	Per 21 CFR 201.57(c)(18), Section 17 must contain information necessary for patients to use the drug safely and	To mitigate administration errors, we recommend including administration

	patients to read the Patient Information.	effectively. We are concerned that omission of this information could lead to administration errors or inappropriate use of Efavirenz, Lamivudine, and Tenofovir Disoproxil Tablets.	instructions in Section 17 that are consistent with Section 2.
Patient Package Insert (PPI)			
9.	We note the use of only degrees Celsius in the "How should I store…" section of the Patient Information.	Degrees Fahrenheit is used and understood more by end users in the US. We are concerned this may cause confusion leading to storage errors.	To mitigate storage errors, we recommend the use of Fahrenheit degrees to describe the storage of Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate tablets in the PPI.
10.	We note additional storage recommendations (i.e. Keep efavirenz, lamivudine and tenofovir disoproxil fumarate tablets in the original container) are included in the PPI but not in the PI, which could cause confusion leading to storage errors.	Discrepancy in the storage statements across the labels and labeling may cause confusion or result in misinterpretation.	To mitigate storage errors, we recommend ensuring the storage statements align across the labels and labeling.

Table 3: Identified Issues and Recommendations for Aurobindo (entire table to be conveyed to Applicant)

Container Labels and Carton Labeling			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
1.	The Fahrenheit temperature is not included in the storage statement which could lead to storage errors.	Fahrenheit temperature is used and understood more by end users in the US.	To mitigate storage errors, we recommend revising the storage statement to read: *Store below 30°C (86°F).*
2.	The container label for Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate Tablets looks almost identical to your container label for Lamivudine and Tenofovir Disoproxil Fumarate Tablets.	Lamivudine and Tenofovir Disoproxil Fumarate Tablets and Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate Tablets are intended to be on the market together. Both drugs contain 2 of the same active ingredients at the same strengths. As depicted below, both container labels currently (b) (4)  (b) (4)	To mitigate wrong drug errors, we recommend you consider (b) (4) for the container label or a contrasting color block to highlight the strength of Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate Tablets that provides adequate differentiation between these two container labels. The same should be applied to the carton labeling.

		(b) (4) We are concerned this may lead to wrong drug errors (e.g. selection errors from the pharmacy shelf).	
3.	An area for the lot number statement and expiration date is not indicated on the container label.	The lot number statement and expiration date is 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 is included on the immediate container label per 21 CFR 201.10(i)(l) and 21 CFR 201.17, respectively. For the expiration date, we recommend using a format like either: DDMMMYYYY (e.g., 31JAN2013) MMMYYYY (e.g., JAN2013) YYYY-MMM-DD (e.g., 2013-JAN-31) YYYY-MM-DD (e.g., 2013-01-31)
4.	We note you include storage recommendations in the Patient Package Insert instructing patients to keep efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets in the original container and to keep the bottle tightly closed; however, this information	If your intent is to convey that Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate Tablets are to be stored in the original container and the bottle be kept tightly closed, then this important information should be consistent across the Prescribing Information (PI), Patient Package	For consistency, we recommend you include the following or similar storage statements on the container label and carton labeling: *"Store in original container. Keep bottle tightly closed."*

	is not included on the container label.	Insert (PPI), container label, and carton labeling. We are concerned omission of this information or discrepancy across the label and labeling could lead to storage errors.	Ensure the storage recommendations are consistent across the PI, PPI, container label, and carton labeling.
General Formatting Recommendations			
5.	Consider adding the statement, *"Keep this and all medication out of the reach of children"* to the side panel of the container label.		

5 CONCLUSION

Our evaluation of the proposed label, labeling, and packaging for Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate Tablets identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 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 4 presents relevant product information for Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate Tablets that Aurobindo Pharma Limited submitted on February 16, 2018.

Table 4. Relevant Product Information for Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate Tablets	
Initial Approval Date	Tentative Approval June 26, 2013
Active Ingredient	efavirenz, lamivudine, and tenofovir disoproxil fumarate
Indication	(b) (4) for the treatment of HIV-1 infection in adults and (b) (4) weighing at least 40 kg
Route of Administration	Oral
Dosage Form	Tablet
Strength	600 mg/300 mg/300 mg
Dose and Frequency	1 tablet daily
How Supplied	Bottles of 30 tablets
Storage	Store below 30°C
Container Closure System	120 cc HDPE bottles with child resistant closure and heat sealed liner

APPENDIX E. RESPONSE TO MARCH 8, 2018 INFORMATION REQUEST

- IR Response received on March 9, 2018

cover-letter.pdf

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 Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate labels and labeling submitted by Aurobindo on February 16, 2018.

- Container label
- Carton labeling
- Prescribing Information (Image not shown)

F.2 Label and Labeling Images

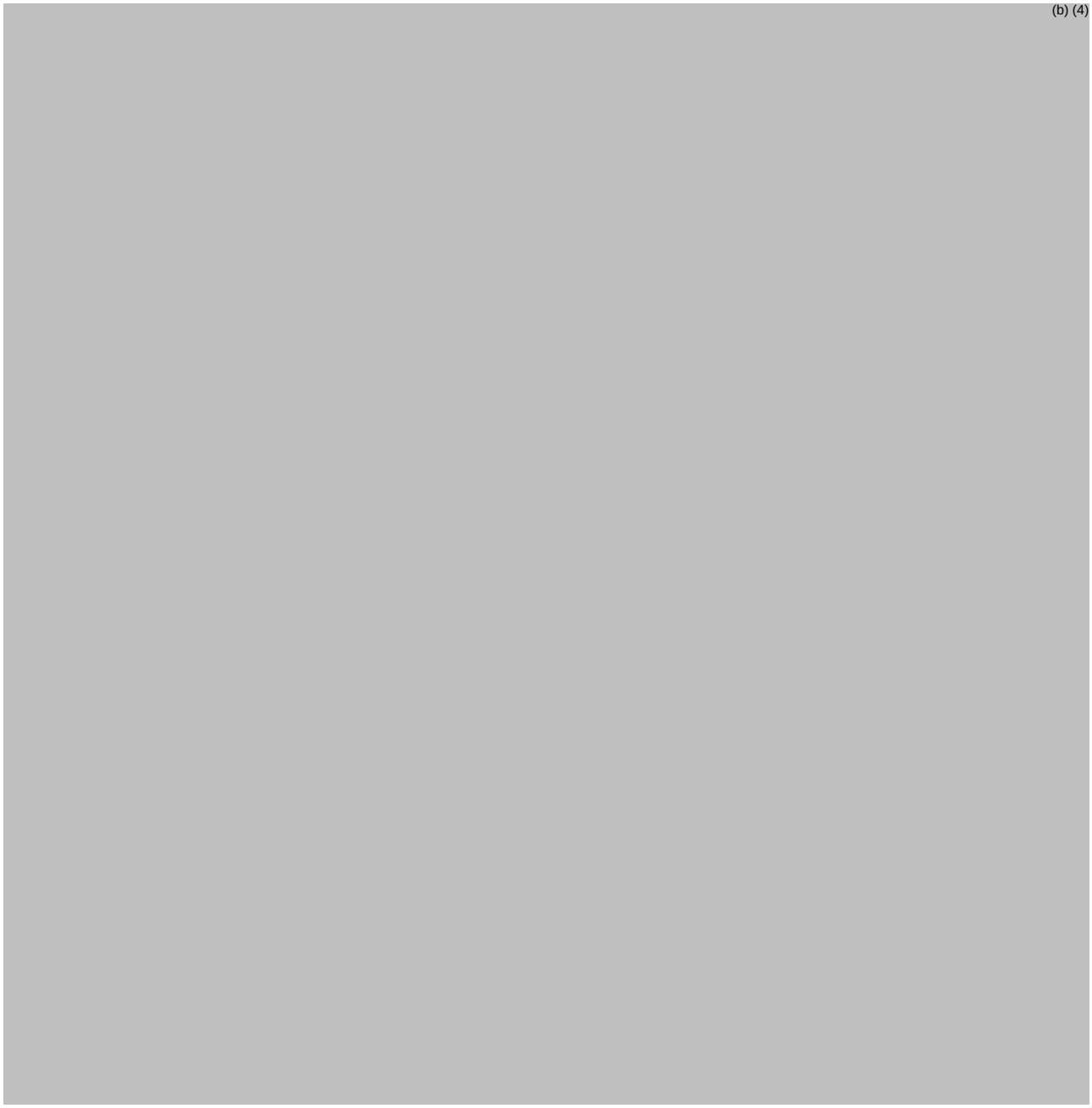
Container Label

(b) (4)

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

Carton Labeling

(b) (4)



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/s/

VALERIE S WILSON
06/27/2018

OTTO L TOWNSEND
06/27/2018

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:	June 14, 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):	Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 022343
Applicant:	Aurobindo Pharma Limited

1 INTRODUCTION

On February 16, 2018, Aurobindo Pharma Limited re-submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 022343 for Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets. 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 June 26, 2013. The proposed indication for Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets is (b) (4) for the treatment of HIV-1 infection in adults (b) (4) weighing at least 40 kg.

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 April 24, 2018, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets.

2 MATERIAL REVIEWED

- Draft Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets PPI received on February 16, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 24, 2018.
- Draft Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets Prescribing Information (PI) received on February 16, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 24, 2018.
- Approved SYMFI LO (efavirenz, lamivudine and tenofovir disoproxil fumarate) tablets comparator labeling dated February 5, 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.

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/

SUSAN W REDWOOD
06/14/2018

WENDY R LUBARSKY
06/14/2018

BARBARA A FULLER
06/14/2018

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

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

Memorandum

Date: June 14, 2018

To: David Araojo, 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 EFAVIRENZ, LAMIVUDINE, and TENOFOVIR DISOPROXIL FUMARATE tablets, for oral use

NDA: 22343

In response to DAVP consult request dated April 24, 2018, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for EFAVIRENZ, LAMIVUDINE, and TENOFOVIR DISOPROXIL FUMARATE tablets, for oral use.

PI and PPI/Medication Guide/IFU: OPDP's comments on the proposed labeling are based on the draft PI and PPI received in the consult request link from DAVP (David Araojo) on April 24, 2018, and we do not have any comments.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on June 14, 2018.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received in the consult request link on April 24, 2018, and we do not have any comments.

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

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/s/

WENDY R LUBARSKY
06/14/2018

M E M O R A N D U M

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

DATE: November 9, 2012

TO: Debra B. Birnkrant, M.D.
Director, Division of Antiviral Products
Office of Antimicrobial Products

FROM: Sripal R. Mada, Ph.D.
Team Leader (Acting)
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering PEPFAR NDA 22-343 Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate Tablet, 600 mg / 300 mg / 300 mg from Aurobindo Pharma Limited, India

At the request of the Division of Antiviral Products (DAVP), the Division of Bioequivalence and GLP Compliance (DBGC) inspected the following BE study:

086-11: "An open label, randomized, two-treatment, two-sequence, two-period, crossover, single-dose comparative oral bioavailability study of fixed dose combination of Efavirenz 600 mg, Lamivudine 300 mg and Tenofovir Disoproxil Fumarate 300 mg tablets (Test) of Aurobindo Pharma Ltd., India and respective reference formulations of [Sustiva 600 mg tablets of Bristol Myers Squibb Company, Epivir 300 mg tablets of GlaxoSmithKline and Viread 300 mg tablets of Gilead Sciences Inc.] USA in 48 healthy, adult, human subjects under fasting conditions"

Clinical:

The inspection of the clinical portion was conducted by Alexander M. Kay (ORA) at **AXIS Clinicals Limited, Hyderabad, India (Axis).**

Following the inspection (October 1-5, 2012), Form FDA-483 was issued (**Attachment 1**). The firm's response was received on October 10, 2012 (**Attachment 2**).

The Form FDA-483 observation, Axis' response to Form FDA-483 and our evaluation follow:

1. The informed consent form (ICF) lacks a description of risks or discomforts to subjects. Specifically, the consent form used for study 086-11 only includes risks associated with the study medications that were listed in the protocol and does not include all of the risks that were in the prescribing information used as the investigator's brochure.
Risks that are not mentioned in the ICF include:
a) Both lamivudine and tenofovir disoproxil fumarate have in the prescribing information a boxed warning regarding lactic acidosis and severe hepatomegaly with steatosis. Neither of these conditions is discussed in the ICF. The prescribing information for efavirenz also warns liver problems, including post marketing reports of hepatic failure in patients with no pre-existing hepatic disease or identifiable risk factors.
b) The prescribing information for both efavirenz and lamivudine indicates a concern of pancreatitis, and the protocol includes specific clinical laboratory testing for this risk, but it is not discussed in the ICF.
c) For efavirenz, the prescribing information states that "… may cause fetal harm when administered during the first trimester to a pregnant woman" and directs "…use of (b) (4) **for 12 weeks after discontinuation…" The ICF does not include any advisory to subjects of this risk or recommendation.**
d) For tenofovir disoproxil fumarate, the prescribing information warns of new onset or worsening renal impairment and decrease in bone mineral density. Risks associated with kidney or bones are not included in the ICF.

In their response to Form FDA-483, Axis stated the prescribing information for EPIVIR, SUSTIVA and VIREAD tablets was provided in the investigator's brochure along with the approved protocol, which was reviewed by the clinical investigator and ethics committee for medical judgment. Axis acknowledged that some risks were not captured in the consent document, because they understood them to be limited to prolonged use of these drugs.

OSI's position is that the ICF appears to have failed to meet the regulatory requirements to inform prospective study subjects under 21 CFR 50.25. If risks are serious enough to be included in black box warnings, those risks should be specified in informed consent documents, unless there is a very good reason to exclude them. While OSI appreciates that the sponsor is appropriately concerned with unnecessarily alarming prospective study subjects, that concern may be addressed by including informative caveats, such as, "These problems have been noted only when patients took the drug for a much longer period of time. We do not think this will be an issue, but we will be testing your blood…," etc. OSI is not aware of any reasons why the black box warnings for these test articles should not be included in the ICF and recommends that the review division evaluate each inspectional finding below, accordingly.

Axis responded to each item presented in Form FDA-483:

- The boxed warning on lactic acidosis for both lamivudine and tenofovir disoproxil fumarate was not included in the ICF, but their signs or symptoms such as nausea, vomiting fatigue, diarrhea, abdominal pain, sleep disorders and nasal symptoms were monitored during the study as part of adverse events.

In the opinion of this reviewer, Axis' response is not adequate for the reasons provided above. Study subjects have a right to know that lactic acidosis has been identified with both study drugs. A more complete disclosure is recommended.

- Severe hepatomegaly with steatosis listed for both lamivudine and tenofovir disoproxil fumarate was not included in the ICF, but liver function tests were monitored for subjects' inclusion and post-study lab investigations.

In the opinion of this reviewer, Axis' response is not adequate for the reasons provided above. Study subjects have a right to know that hepatomegaly with stenosis has been identified with both study drugs. A more complete disclosure is recommended.

- Axis stated they did not enroll female subjects for this study; therefore, discussion of fetal risks was not applicable.

In the opinion of this reviewer, Axis' response is adequate.

- Risks associated with kidney or bones are not included in the ICF, but these were monitored by renal function tests during subjects' inclusion and post-study lab investigations.

In the opinion of this reviewer, Axis' response is not adequate for the reasons provided above. A more complete disclosure is recommended.

Analytical:

The inspection of analytical portion was conducted by Sripal R. Mada, Ph.D (OSI) at (b) (4)

Following the inspection (b) (4), Form FDA-483 was issued (**Attachment 3**). The firm's response was received on October 04, 2012 (**Attachment 4**).

The Form FDA-483 observation, (b) (4) response to Form FDA-483 and our evaluation follow:

1. **Failure to evaluate long term freezer stability at -70^{0}C for efavirenz in the presence of lamivudine and tenofovir. Study subjects were treated with efavirenz, lamivudine and tenofovir.**

In their response to Form FDA-483, (b) (4) provided additional long term freezer stability for 502 days at -70^{0}C for efavirenz in the presence of lamivudine and tenofovir.

In the opinion of this reviewer, (b) (4) response is adequate.

2. Failure to evaluate potential interference by efavirenz on the quantification of lamivudine and tenofovir.

In their response to Form FDA-483, (b) (4) provided results of an experiment on potential interference by efavirenz on quantification of lamivudine and tenofovir. The data indicated that lamivudine and tenofovir peaks were not affected by the presence of efavirenz.

In the opinion of this reviewer, (b) (4) response is adequate.

Conclusion:

The DBGC reviewer recommends that the clinical and analytical data from this study are acceptable for your review. However, the Medical Reviewer should evaluate the Axis response concerning the informed consent issues.

Sripal R. Mada, Ph.D.
Team Leader (Acting), Bioequivalence Branch, DBGC, OSI

Final Classifications:

VAI - AXIS Clinical Limited, Hyderabad, India
FEI: 3006649033

VAI - (b) (4)

cc:
OSI/Moreno
OSI/DBGC/Taylor/Dejernett
OSI/DBGC/BB/Haidar/Mada
OSI/DSC/Parker/Prohaska
OND/OAP/DAVP/Araojo/Birnkrant
OCP/DCP4/Lazor
ORA/SEA-DO/Kay
Draft: SRM 10/25/2012
Edit: MFS 10/26/2012; SHH 11/08/2012; CEP 11/08/2012; WHT 11/09/2012
OSI: 6351; O:\Bioequiv\EIRCover\22343.aur.efa
FACTS: (b) (4)

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SRIPAL R MADA
11/09/2012

WILLIAM H TAYLOR
11/09/2012