CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208255Orig1s000

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	**January 29, 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 208255, resubmission dated July 25, 2017**
Original Regulatory Action and Date	**PEPFAR, Tentative Approval (TA) on March 10, 2017**
Applicant	**Mylan Pharmaceuticals Inc.**
U.S. Agent	**N/A, U.S. based**
Letter Date	**July 25, 2017**
Stamp Date	**July 25, 2017**
Goal Date	**January 25, 2018**
Established Name	**Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate**
Proprietary Name	**Symfi Lo**
Dosage Form/Strength	**Tablets, 400 mg/300 mg/300 mg**
Subject	**Class 2 Resubmission to a TA, Requesting Final Approval**
Materials Reviewed	➢ **Electronic Resubmission dated July 25, 2017** ➢ **Current U.S. labeling for SUSTIVA (efavirenz), EPIVIR (lamivudine) and VIREAD (tenofovir disoproxil fumarate), TA label for NDA 208255** ➢ **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

Mylan Pharmaceutical Inc's (Mylan) original 505(b)(2) NDA 208255 for Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate Tablets, 400 mg/300 mg/300 mg, was reviewed under the President's Emergency Plan for AIDS Relief (PEPFAR) and granted tentative approval on March 10, 2017.

On July 25, 2017, Mylan submitted a class 2 resubmission requesting final approval and marketing in the United States. The applicant requested approval: 1) following expiration of pediatric exclusivity associated with referenced NDA 21356 for Viread Tablets, 2) prior to the expiration of D-147 exclusivity associated with referenced NDA 20564 for Epivir

Tablets (by removing label information related to the D-147 exclusivity), and 3) prior to the expiration of patents associated with referenced NDA 21360 for Sustiva Tablets (Mylan has been granted license to the associated Sustiva patents).

Mylan's proposed indication for use alone as a complete regimen for the treatment of HIV-1 infection in adults was revised by DAVP to patients 12 years of age and older and weighing at least 35 kg due to the D-147 exclusivity for referenced Epivir Tablets. However, it was determined that 3-year exclusivity for Epivir was granted in error. Thus, it was not necessary to consider the exclusivity implications, if any, for purposes of this approval. The indicated population was revised to adults and pediatric patients weighing at least 35 kg.

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, Viread Tablets, and the March 10, 2017, tentatively approved label for this FDC. 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.

Additionally, DMEPA has reviewed the proposed proprietary name, Symfi Lo, and concluded that the name is acceptable.

Please refer to the following related reviews for NDA 208255:

- OPQ, dated January 20, 2018
- DPMH
- DMEPA, dated October 18, 2017, December 21, 2017, and January 19, 2018
- OMPI, dated December 29, 2017
- OPDP, dated December 29, 2017

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 35 kg."

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

3. Addition to CONTRAINDICATIONS:

SYMFI LO 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.xx 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 SYMFI LO, should be used with caution. Treatment with SYMFI LO 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.xx)].*

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 SYMFI LO as a fixed dose tablet in pediatric patients infected with HIV-1 and weighing at least 35 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. Mylan has adequately responded to the Division's labeling revisions for the label conveyed on February 1, 2018, via email correspondence; therefore, an approval action is warranted.

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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 and this page is the manifestation of the electronic signature.

/s/

DAVID E ARAOJO
02/02/2018

JEFFREY S MURRAY
02/02/2018

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
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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:	208255
Sponsor:	Mylan Pharmaceuticals, Inc.
Drug:	Symfi Lo [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 (400-mg, 300-mg, 300-mg) oral tablet
Reference Products:	Sustiva (EFV), NDA 021360, Bristol-Myers Squibb Company Epivir (3TC), NDA 020564, ViiV Healthcare Viread (TDF), 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 4 mg/kg orally twice daily or 8 mg/kg 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 table is appropriate.]

Viread:
In combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and 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 based on body weight), once daily.]

Proposed Indication: For use alone as a complete regimen for the treatment of HIV-1 infection in patients older than 17 years of age.

Consult Request: The Division of Antiviral Products (DAVP) requests DPMH's input on the proposed labeling for 505(b)(2), a class 2 resubmission for NDA 208255 for EFV/3TC/TDF (400-mg/300-mg /300 mg) fixed-dose, oral tablet by Mylan Pharmaceuticals, Inc. (consult dated December 6, 2017). Per the Consult, labeling for this 505(b)(2) application proposes to carve out what the sponsor believed to be protected pediatric information based on exclusivity for NDA 20564 (Epivir) that expires on March 23, 2018. DAVP requests DPMH assistance on determining whether any protected pediatric information should be retained or added, and whether a disclaimer statement is appropriate. We note that it was subsequently determined that 3-year exclusivity for Epivir was granted in error; and it was not necessary to consider the implications, if any, of this exclusivity for purposes of this approval.

Background:
The labeling under review is for Symfi Lo, a new fixed-dose combination of three approved antiretroviral drug products, EFV/3TC/TDF (400-mg, 300-mg, 300-mg), under the new drug application (NDA) 208255, a 505(b)(2), manufactured by Mylan Pharmaceuticals, Inc. On March 10, 2017, DAVP granted NDA 208255 a Tentative Approval (TA) under the expedited review provisions of the President's Emergency Plan for AIDS Relief (PEPFAR).[1,2] On July 25, 2017, the sponsor submitted a class 2 resubmission, 505(b)(2) application seeking full approval of NDA 208255 for EFV/3TC/TDF (400-mg/300-mg/300-mg) oral tablet.

Because this product will be the first fixed-dose combination tablet approval for these three antiretroviral drug products, the proposed new formulation triggers the PREA. However, all PREA study requirements and WR, where applicable, for each individual component of this fixed dose combination product have been fulfilled. This new fixed-dose combination product was discussed at the Pediatric Review Committee (PeRC) on July 12, 2017 and PeRC concurred with a partial waiver on pediatric patients weighing less than 35 kg because this product fails to represent a meaningful therapeutic benefit over existing therapies. Therefore, pediatric assessments on pediatric patients weighing less than 35 kg will be required to be submitted for the planned 505(b)(2), NDA 208255.

[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] NDA 208255 Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, 400-mg/300-mg/300-mg, by Mylan Pharmaceuticals, Inc. Tentative Approval letter from DAVP (dated March 10, 2017).

This fixed dose combination product will be fully assessed for pediatric patients weighing at least 35 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[3]

SUSTIVA (efavirenz)
- February 1, 2002: Approved as a non-nucleoside reverse transcriptase inhibitor (NNRTI) indicated in combination with other antiretroviral agents for treatment of HIV-1 infection in adults.
- May 5, 2013: Approved in pediatric patients at least 3 months old and weighing at least 3.5 kg
    - FDA waived the Pediatric Equity Research Act (PREA) pediatric study requirement for ages 0 to less than 3 months because the product would be ineffective and/or unsafe in this age group.
    - 3-year Hatch-Waxman was granted on May 5, 2013 and expired on May 2, 2016. Sustiva labeling, Section 2. Dosage and Administration, (2.3) in pediatric patients 3 months of age or older and weighing between 3.5 kg and 40 kg based on patient body weight and the recommended number of tablets. The 400-mg tablet is recommended for pediatric patients weighing at least 32.5 kg (see the **Appendix**, **Table 1** Sustiva Dosing in Pediatric Patients by Body Weight).

EPIVIR (lamivudine)
- April 11, 1997: Approved as a NRTI indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults.
- June 24, 2002: Labeling was revised to add pediatric use information on the oral solution based on the Clinical Endpoint Study in Pediatric Patients (Study ACTG300), a multicenter, randomized, double-blind study that provided comparison of Epivir plus Retrovir (zidovudine) to didanosine monotherapy (this study pre-dates enactment of PREA).
- February 1, 2008: A supplemental (s) sNDA provided dosing of Epivir scored tablets (150 mg) in pediatric patients weighing at least 14 kg and who can swallow a solid tablet (this supplement did not trigger PREA).
- March 23, 2015: A pediatric efficacy supplement supported labeling revisions to Section 2. Dosing and Administration for pediatric patients 3 months and older.
    - Because Epivir is labeled for pediatric patients aged 3 months to 17 years for the treatment of HIV-1 infection, no additional pediatric studies are needed.
- July 20, 2016: Labeling updated pediatric use information on virologic suppression and resistance information for the (oral solution) based on the Anti-Retroviral Research for Watoto (ARROW) trial (COL105677) conducted in Africa that assessed the safety of once-daily compared with twice-daily dosing of EPIVIR in pediatric patients 3 months to less than 17 years of age with HIV-1 infection.
    - Updates to Warnings and Precautions, Use in Specific Populations, Pediatric Use, Clinical Pharmacology, Microbiology, and the Clinical Studies, Pediatric Studies sections include virologic suppression and resistance information (oral solution) cited above. Virologic suppression was demonstrated to be higher with the scored tablet than with the (oral solution). The scored tablet is preferred, if a patient weighs more than 14 kg and can

[3] Although this review notes exclusivities listed in the Orange Book, it was not necessary to consider the impact, if any, on the approval of this product because the exclusivities have since expired or determined to be granted in error.

swallow a tablet (see the **Appendix**, **Table 2**, Epivir Recommended Dosage for Pediatric Patients).

VIREAD (tenofovir disoproxil fumarate)

- October 26, 2001: Approved as a nucleotide analog HIV-1 reverse transcriptase inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults.
- March 24, 2010**:** Approved in pediatric patients greater than or equal to 12 years of age and weighing at least 35 kg. Section 2.1 describes the recommended dose in adults and pediatric patients 12 years of age and older (35 kg or more) as one 300 mg Viread tablet taken orally once daily (see the **Appendix**, Viread Dosing Recommendations in Pediatric Patients).
    - Orphan Exclusivity (7-years) was granted upon the approval dated March 24, 2010 for the treatment of HIV infection in combination with other antiretroviral agents in patients 12 years to less than 18 years of age and expired on March 24,2017. An additional 6 months of Pediatric Exclusivity expired on September 24, 2017.
    - A use patent for Viread in HIV expired on January 25, 2018 for treatment of HIV-I infection in combination with one or more additional antiviral agents.
- January 18, 2012: Approved in pediatric patients 2 years to less than 12 years of age. Section 2.2 Recommended Dose in Pediatric Patients 2 Years to Less than 12 years of Age with HIV-infection recommends an oral dose of Viread as 8-mg of tenofovir disoproxil fumarate (tenofovir DF) per kg of body weight (up to a maximum of 300 mg) once daily administered as (the powder or) tablets. Viread is available as tablets (150, 200, 250, and 300 mg strengths) for pediatric patients weighing at least 17 kg and who can swallow a tablet (see the **Appendix, Table 3**, dosing for pediatric patients ≥ 2 years of age and weighing ≥ 17 kg). These studies were conducted under WR originally issued on December 21, 2001 and last amended on September 16, 2010.
    - This additional pediatric use labeling was supported by two randomized trials with Viread in pediatric HIV-1 infected patients 2 years to less than 18 years of age including a PK study demonstrating that the recommended doses of tenofovir are similar to that found to be safe and effective in adult clinical trials with Viread.
    - 3-year Hatch-Waxman was granted upon approval (see above) on January 18, 2012 and expired on January 18, 2015. An additional 6 months of Pediatric Exclusivity was granted on September 7, 2011 for meeting the terms of the WR and expired on July 18, 2015.

As cited earlier in this review, Mylan Pharmaceuticals, Inc, submitted a class 2 resubmission [request for approval of 505(b)(2), NDA 208255 for the fixed dose combination product EFV/3TC/TDF (400-mg, 300-mg, 300-mg) tablet] that was tentatively approved on March 20, 2017. The sponsor's proposed labeling excludes all pediatric study results (ARROW trial in pediatric patients 3 months to 17 years of age) because the sponsor believed the information was protected by exclusivity. See Epivir labeling, Section 8.4 Pediatric Use and Section 14.2 Pediatric Subjects that refer to data from the ARROW trial. It was determined that 3-year exclusivity for Epivir was granted in error. Thus, it was not necessary to consider the exclusivity implications, if any, for purposes of this approval.

DPMH concludes that based on the strength of the individual ingredients in the proposed fixed dose (400 mg EFV, 300 mg 3TC and 300 mg TDF), pediatric dosing information should be based on weight and would be appropriate for pediatric patients weighing more than 35 kg. Viread (3TC) is the drug product that establishes the limit on weight-based dosing. Sustiva (EFV), approved labeling, Section 2. Dosage and Administration, recommends a 400-mg daily dose of efavirenz for a pediatric patient weighing at least 32.5 kg to less than 40 kg. Epivir (3TC) 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) tablets are approved for pediatric

patients 12 years and older who weigh at least 35 kg to be administered a dosage of 300 mg once daily. Use patents for Viread expired on January 25. 2018 and will not impact the regulatory pathway to approval for this fixed-dose tablet, EFV/3TC/TDF (400-mg, 300-mg, 300-mg).

Therefore, DPMH recommends that this proposed 505(b)(2), fixed-dose combination tablet include a weight limitation (of at least 35 kg body weight) in labeling Section 1. Indications and Usage, Section 2. Dosage and Administration, (subsection 2.3), and Section 8. Use in Specific Populations, subsection 8.4 Pediatric Use for pediatric patients with HIV-1 infection.

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. DPMH recommends that the pediatric use information statement include pediatric patients who weigh at least 35 kg and who can swallow an oral tablet.

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 that is not protected for efavirenz, lamivudine, and tenofovir disoproxil fumarate.

Reference products, Sustiva (NDA 021360), Epivir (NDA 020564), and Viread (NDA 021356) most recent FDA-approved pediatric use information are summarized in the **Background, Regulatory History** section of this review. DPMH recommendations for this 505(b)(2) NDA 208255, Symfi Lo tablet, EFV/3TC/TDF (400-mg, 300-mg, 300-mg) by Mylan Pharmaceuticals, Inc. reflect labeling initially provided to the DAVP on December 20, 2017, to the sponsor on January 12, 2018, and revised labeling based on internal discussions that included DPMH and DAVP on January 19, 2018.

DPMH notes that (b) (4) We believe that the Mylan Pharmaceuticals, Inc. 505(b)(2) application can be approved with appropriate revisions to the sponsor's proposed labeling because this fixed dose combination product can be used by pediatric patients weighing at least 35 kg. (b) (4) 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

SYMFI LO (b) (4) is a three-drug (b) (4) combination of (b) (4) ~~(~~efavirenz~~)~~, a non-nucleoside reverse transcriptase inhibitor and (b) (4) ~~(~~lamivudine and tenofovir disoproxil fumarate, both nucleo(t)side reverse transcriptase inhibitors and is indicated (b) (4) as a complete regimen for the treatment of human immunodeficiency virus type 1

[4] NDA 208255 Symfi Lo (EFV, 3TC, TDF) tablet (400 mg, 300 mg, 300 mg) received by the DAVP on July 25, 2017.

(HIV-1) infection in [redacted] adult patients [redacted] and pediatric patients [redacted] weighing at least 35 kilograms.

Reviewer's Comments:
DPMH recommends that the indication section reflect that dosage limitation is based on body weight as detailed earlier in this review.

WARNINGS AND PRECAUTIONS

- Pancreatitis: Use with caution in pediatric patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue SYMFI LO as clinically appropriate. (5.xx)

Reviewer's Comments:
DPMH agrees that the WARNINGS AND PRECAUTIONS section include the serious risk of pancreatitis in pediatric patients with a history of pancreatitis or other risk factor for pancreatitis. Numbering of each Warnings and Precautions needs to be updated sequentially.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SMYFI LO (efavirenz, lamivudine and tenofovir disoproxil fumarate) is indicated [redacted] as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adult [redacted] and pediatric patients who weigh at least 35 kilograms.

Reviewer's Comments: DPMH rationale for revisions to Section 1. Indications and Usage are based on pediatric body weight of at least 35 kg.

2 DOSAGE AND ADMINISTRATION

2.2 [redacted] Recommended Dosage for Adult [redacted] and Pediatric Patients Weighing at least 35 kilograms

SYMFI LO is a three-drug fixed dose combination product containing 400 mg of efavirenz (EFV), 300 mg of lamivudine (3TC), and 300 mg of tenofovir [redacted] fumarate (TDF). The recommended dosage of SYMFI LO in HIV-1-infected adults [redacted] is [redacted] one tablet taken orally, once daily [redacted] SYMFI LO tablets 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)* [redacted]

Reviewer's Comments: As cited earlier in this review, DPMH recommends revisions to Section 2. Dosage and Administration to include pediatric patients who weigh at least 35 kg and can swallow a tablet.

5 WARNINGS AND PRECAUTIONS

5.xx Pancreatitis
In pediatric patients with a history of prior antiretroviral nucleotide exposure, a history of

pancreatitis, or other significant risk factors for the development of pancreatitis, 3TC, a component of SYMFI LO, should be used with caution. Treatment with SYMFI LO should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur. *[see Adverse Reactions (6.1)]*

Reviewer Comments: DPMH agrees with the addition of Pancreatitis to Warnings and Precautions section of labeling based on safety information with Epivir (lamivudine). DPMH defers to DAVP to sequentially order numbering in Warnings and Precautions with the addition of the risk of pancreatitis.

6.1 Clinical Trials Experience

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 retroviral agents. (b) (4) *[see Warnings and Precautions (5.xx)].*

Reviewer Comment: DPMH agrees with addition of safety information on pancreatitis and the reported events in pediatric patients.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

(b) (4)

The safety and effectiveness of SYMFI LO as a fixed dose tablet in pediatric patients infected with HIV-1 and weighing at least 35 kg have been established based on clinical studies using the individual components (efavirenz, lamivudine, and tenofovir disoproxil fumarate) (b) (4)

Reviewer's Comments:
DPMH recommends revising the first sentence as shown above to inform that this pediatric labeling for pediatric patients with HIV-1 and weighing at least 35 kg is based on clinical studies using the approved individual components (efavirenz, lamivudine, and tenofovir disoproxil fumarate).

17 PATIENT COUNSELING INFORMATION

Pancreatitis: Advise patients or guardians to monitor pediatric patients for signs and symptoms of pancreatitis [see Warnings and Precautions (5.xx)]

Reviewer Comment: DPMH agrees with adding pancreatitis to the list of serious risks associated with use of Symfi Lo, a fixed-dose combination tablet.

General Comments

DPMH reviewed the sponsor's proposed labeling for Symfi Lo (EFV/3TC/TDF) (400-mg, 300-mg, 300-mg) tablet, a 505(b)(2) submission under NDA 208255 by Mylan Pharmaceuticals, Inc, and participated in internal meetings on December 20, 2017 and January 19, 2018. Labeling recommendations were provided in track changes for DAVP to revise the Symfi Lo 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 the sponsor, may differ from the recommendations in this DPMH labeling review.

APPENDIX:

See the individual product labeling from Section 2. Dosage and Administration, as applies to pediatric patients.

Highlighted patient weight and recommended dosage support proposed labeling for this new fixed-dose combination tablet.

SUSTIVA (efavirenz)

Subsection 2.3 Pediatric Patients

Table 1. Sustiva Dosing in Pediatric Patients

Patient Body Weight	Sustiva 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: Sustiva labeling, Section 2.3, Table 1. (approved October 2017)		

EPIVIR (lamivudine)

Subsection 2.2 Recommended Dosage for Pediatric Patients

Table 2. Recommended Dosage for 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: Epivir labeling, Section 2.2, Table 1. (approved July 2016).				

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

VIREAD (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 Viread 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: Viread labeling, Section 2.2, Table 1. (approved April 2017)	

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/s/

CAROLYN L YANCEY
02/02/2018

JOHN J ALEXANDER
02/02/2018
I concur and am signing for Dr. Sachs

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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)

Date of This Memorandum:	January 19, 2018
Requesting Office or Division:	Division of Antiviral Products (DAVP)
Application Type and Number:	NDA 208255
Product Name and Strength:	Symfi Lo (efavirenz, lamivudine, and tenofovir disoproxil fumarate) Tablets; 400 mg/300 mg/300 mg
Applicant/Sponsor Name:	Mylan Pharmaceutical Inc.
FDA Received Date:	January 18, 2018
OSE RCM #:	2017-2076-1
DMEPA Safety Evaluator:	Valerie S. Wilson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMO

The Division of Antiviral Products requested that we review the revised container labels and carton labeling for Symfi Lo (Appendix A) to determine if they are acceptable from a medication error perspective. Some of the revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container label and carton labeling for Symfi Lo are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Wilson, V. Label and Labeling Review for Symfi Lo (NDA 208255). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 DEC 21. RCM No.: 2017-2076.

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/s/

VALERIE S WILSON
01/19/2018

OTTO L TOWNSEND
01/19/2018

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:	December 28, 2017
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):	TRADENAME (efavirenz, lamivudine and tenofovir disoproxil fumarate)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 208255
Applicant:	Mylan Pharmaceuticals Inc.

1 INTRODUCTION

On July 25, 2017, Mylan Pharmaceuticals Inc. re-submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 208255 for TRADENAME (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 March 10, 2017. The proposed indication for TRADENAME (efavirenz, lamivudine and tenofovir disoproxil fumarate) is as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in patients (b) (4)

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 October 12, 2017, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TRADENAME (efavirenz, lamivudine and tenofovir disoproxil fumarate) tablets.

2 MATERIAL REVIEWED

- Draft TRADENAME (efavirenz, lamivudine and tenofovir disoproxil fumarate) PPI received on July 25, 2017 and received by DMPP and OPDP on December 7, 2017.
- Draft TRADENAME (efavirenz, lamivudine and tenofovir disoproxil fumarate) Prescribing Information (PI) received on July 25, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 7, 2017 and December 20, 2017.

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)

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
12/28/2017

WENDY R LUBARSKY
12/29/2017

BARBARA A FULLER
12/29/2017

LASHAWN M GRIFFITHS
12/29/2017

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

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

Memorandum

Date: December 29, 2017

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 TRADENAME™ (efavirenz, lamivudine and tenofovir disoproxil fumarate) tablets, for oral use

NDA: (b) (4)

In response to DAVP consult request dated October 12, 2017, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA/BLA submission for TRADENAME™ (efavirenz, 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 (David Araojo) on December 20, 2017, and are provided below in the HIGHLIGHTS, CLINICAL STUDIES, and PATIENT COUNSELING INFORMATION sections.

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 December 29, 2017.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on December 7, 2017, 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 .

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/s/

WENDY R LUBARSKY
12/29/2017

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:	December 21, 2017
Requesting Office or Division:	Division of Antiviral Products
Application Type and Number:	NDA 208255
Product Name and Strength:	Symfi Lo (efavirenz, lamivudine, and tenofovir disoproxil fumarate) Tablets, 400 mg/300mg/300 mg
Product Type:	Multi-ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Mylan Pharmaceuticals, Inc.
Submission Date:	July 25, 2017 and December 7, 2017
OSE RCM #:	2017-2076
DMEPA Safety Evaluator:	Valerie S. Wilson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 REASON FOR REVIEW

This review responds to a request from the Division of Antiviral Products to review the proposed label and labeling for Symfi Lo to identify areas of vulnerability that may lead to medication errors.

On March 10, 2017, NDA 208255 was granted Tentative Approval for Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate fixed-dose 400 mg/300 mg/300 mg tablets under the expedited review provisions of the President's Emergency Plan for AIDS Relief (PEPFAR)[a].

At this time, Mylan Pharmaceutical Inc. is requesting Final Approval of NDA 208255 and therefore submitted revised prescribing information, patient information, and proposed container label and carton labeling for Agency review.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material 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
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

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

[a] Murray, J. Tentative Approval for Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate. Silver Spring (MD): FDA, CDER, OND, DAVP (US); 2017 March 10. NDA 208255.

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We evaluated the proposed Prescribing Information, Patient Package Insert (PPI), container labels, and carton labeling for NDA 208255 and identified several issues, which are discussed in Tables 2 and 3.

Table 2. Identified Issues and Recommendations for the Division

	Identified Issue	Rationale for Concern	General Comments and DMEPA Recommendations for the Division
Prescribing Information			
General			
1.	Use of the placeholder "TRADENAME" throughout the label.	The proposed proprietary name, Symfi Lo, was found conditionally acceptable on October 18, 2017.[b]	Replace the placeholder "TRADENAME" with the conditionally acceptable proprietary name, Symfi Lo.
Dosage and Administration			
2.	In the RECOMMENDED DOSAGE section of the PI, we note the recommended dosage statement includes the strength (b) (4)	As currently stated, the recommended dosage statement in section 2 (b) (4)	Consider revising the recommended dosage statement in section 2 to read, "The recommended dosage of Symfi Lo in HIV-1 infected adults is 1 tablet orally, once daily."
How Supplied/Storage and Handling			
3.	Per the July 25, 2017 cover letter, Mylan states the product will be distributed using child-resistant closures in the United States. (b) (4)	(b) (4)	Consider revising the description of the packaging configuration to include "child-resistant closure," for example, to read: "cartons containing bottles of 30 tablets with desiccant, induction seal, and child-resistant (b) (4)

[b] Wilson, V. Proprietary Name Review for Symfi and Symfi Lo. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 OCT 18. Panorama No.: 2017-16575934 and 2017-16639499.

	(b) (4)	(b) (4)	Given that Symfi Lo is intended to be dispensed in its original container and a PPI is proposed, a similar statement should be included in the PPI. For example, "Symfi Lo comes in a child-resistant package." We defer to the Patient Labeling Team to determine the appropriateness of the above statement.
Patient Counseling Information			
4.	We note section 17 is (b) (4)	(b) (4)	To mitigate wrong administration technique medication errors and to be in alignment with the DOSAGE AND ADMINISTRATION section, we recommend including specific instruction to advise patients to take Symfi Lo on an empty stomach.
Patient Packet Insert			
5.	We note the missed dose statement does not provide clear instruction to not take 2 doses or double a dose of Symfi Lo to make up for a missed dose.	Misinterpreting the missed dose statement could result in accidental overdose of Symfi Lo.	We recommend the missed dose statement be revised to include, for example, "Do not take 2 doses at the same time" or include additional clarifying instruction, for example, "If it is less than 12 hours from the time of your next scheduled dose, do not take the missed dose." We defer to the patient labeling team to determine the appropriateness of the recommended language.

[c] Guidance for Industry: Packaging Statements in Drug Product Labeling. Food and Drug Administration. 2017. Available from https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm569607.pdf

Table 3. Identified Issues and Recommendations for Mylan Pharmaceuticals, Inc

Container Label/Carton Labeling			
	Identified Issue	**Rationale for Concern**	**DMEPA Recommendations for Mylan Pharmaceuticals, Inc**
1.	(b) (4)	(b) (4)	To mitigate the risk of product selection error, (b) (4) Symfi Lo (efavirenz, lamivudine, and tenofovir disoproxil fumarate) Tablets 400 mg/300 mg/300 mg Likewise, make the same revisions to the carton labeling.
2.	(b) (4)		

4 CONCLUSION & RECOMMENDATIONS

DMEPA's evaluation of the prescribing information, patient package Insert (PPI), container label, and carton labeling for Symfi Lo identified several areas that can be improved to prevent medication errors or provide clarity. Table 2 includes our recommendations pertaining to the prescribing information and PPI for the Division's consideration. We ask that Table 3 be conveyed to the Applicant so that DMEPA's recommendations are implemented prior to the approval of NDA 208255.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Symfi Lo that Mylan Pharmaceutical, Inc. submitted on July 25, 2017.

Table 2. Relevant Product Information for Symfi Lo	
Initial Approval Date	Tentative Approval – March 10, 2017
Active Ingredient	efavirenz, lamivudine and tenofovir disoproxil fumarate
Indication	Indicated (b) (4) as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults
Route of Administration	Oral
Dosage Form	Tablet
Strength	400 mg/300 mg/300 mg
Dose and Frequency	400 mg/300 mg/300 mg orally, once daily. It is recommended TRADEMARK tablets be taken on an empty stomach, preferably at bedtime.
How Supplied	Bottles of 30 tablets
Storage	Store below 30°C (86°F). Dispense in original container
Container Closure System	Bottle with a child-resistant closure with desiccant and induction seal

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 5, 2017, we searched DMEPA's previous reviews using the terms, NDA 208255 and efavirenz, lamivudine, and tenofovir disoproxil fumarate. Our search did not identify any previous reviews. We confirmed DMEPA was not previously involved with label and labeling reviews for the Tentative Approval of NDA 208255.

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VALERIE S WILSON
12/21/2017

OTTO L TOWNSEND
12/21/2017

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: **March 7, 2017**

TO: **NDA 208255**
Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate Tablets, 400 mg/300 mg/300 mg

FROM: **David Araojo, Pharm.D.**
Senior Program Coordinator
Division of Antiviral Products (DAVP)

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

SUBJECT: **CSO Labeling Review**

I. Background

The purpose of this submission is to gain tentative approval of Mylan Pharmaceutical Inc's (Mylan) drug application for the following product:

- Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate Tablets, 400 mg/300 mg/300 mg

The availability of a wide range of safe and effective antiretroviral (ARV) drug products is hoped to facilitate a wider distribution of anti-HIV drugs to better meet the demands of the global HIV/AIDS pandemic. Although many antiretroviral drug product versions of previously approved ARVs cannot be currently marketed in the United States 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 (PEPFAR) will consider procurement of products reviewed by FDA that have been granted approval or tentative approval. These products may be distributed outside the United States, depending on regulatory requirements in other countries.

Mylan's application was submitted, for review under the PEPFAR program, as a 505(b)(2) NDA for a fixed dose combination tablet (FDC) containing efavirenz, lamivudine, and tenofovir disoproxil fumarate. The safety and efficacy of the U.S. approved reference listed drugs Sustiva® (efavirenz), Epivir®, (lamivudine) and Viread® (tenofovir disoproxil fumarate) as part of a highly active antiretroviral therapy (HAART) regimen are supported by previously conducted adequate and well- controlled studies. Because the reference listed drugs for the proposed fixed-dose combination product has

unexpired patents or exclusivities, the application cannot be approved but is eligible to receive tentative approval. This FDC uses the U.S. approved dose of 300 mg each for lamivudine and tenofovir disoproxil fumarate and a lower dose, 400 mg, of efavirenz instead of the U.S. approved 600 mg efavirenz dose. The lower 400 mg efavirenz dose is supported by a referenced clinical trial, ENCORE1.

II. Labeling Review

The revised 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 Sustiva® (efavirenz), Epivir®, (lamivudine) and Viread® (tenofovir disoproxil fumarate). Additionally, clinical information supported by the ENCORE1 trial was added to the label.

Please see attachment below for FDA proposed label and edits.

III. Recommended Regulatory Action

Both the revised Prescribing Information and Patient Information were reviewed, and accepted by the applicant, and should allow for the safe and effective use of this fixed dose combination drug product of Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate Tablets, 400 mg/300 mg/300 mg. The applicant has adequately responded to the Division's labeling revisions; therefore, a tentative approval action is recommended.

_____

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

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/s/

DAVID E ARAOJO
03/09/2017

JEFFREY S MURRAY
03/09/2017

Clinical Inspection Summary

Date	January 6 , 2017
From	Antoine El Hage, Ph.D. /OSI/DCCE/GCPAB Susan Thompson, M.D. /OSI/DCCE/GCPAB, Team Leader Kassa Ayalew, M.D., MPH. /OSI/DCCE/GCPAB, Branch Chief
To	David Araojo, Pharm.D, M.S. Regulatory Health Project Manager Kirk Chan-Tack, M.D., Medical Reviewer Adam Sherwat, M.D. Team Leader/ CTDL Division of Antiviral Products (DAVP)
NDA #	NDA 208255
Applicant	Mylan Pharmaceuticals, Inc.
Drug	Efavirenz, lamivudine, and tenofovir disoproxil fumarate tablets
NME (Yes/No)	No
Therapeutic Classification	Priority
Proposed Indication(s)	Treatment of (b) (4) HIV infected individuals
Consultation Request Date	September 19, 2016
Summary Goal Date	February 13, 2017
Action Goal Date	March 13, 2017
PDUFA Date	March 13, 2017
cc:	Central Doc. Rm. NDA 208255 DAVP /Division Director/Debra Birnkrant DAVP /Medical Team Leader/Adam Shewart DAVP /Project Manager/David Araojo DAVP/Medical Officer/Kirk Chun-Tack OSI/Office Director/David Burrow OSI/DCCE/ Division Director/ Ni Khin OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew OSI/DCCE/GCPAB/Team Leader/Susan Thompson OSI/DCCE/GCPAB/ Reviewer/ Antoine El Hage OSI/ GCP Program Analysts/ Yolanda Patague/ Joseph Peacock OSI/Database PM/Dana Walters

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspections for this NDA were conducted at three foreign clinical sites. The inspection of the three clinical investigators listed below revealed no regulatory violations.

The preliminary classification for Drs. Phanuphak, Orrell and Young is No Action Indicated (NAI). No regulatory violations were noted. Data from these sites are acceptable for use in support of the pending application.

The final classification for the above three sites will be made at a later date after receiving and reviewing the EIRs provided by the field investigators. An inspection summary addendum will be generated if conclusions change upon receipt and review of the pending EIRs.

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Based on the inspections of the three clinical sites, the inspectional findings support validity of the data as reported by the sponsor under this NDA.

II. BACKGROUND

Efavirenz (EFV, Sustiva) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that has demonstrated a potent antiretroviral activity. The superior efficacy of EFV together with the high pill burden and toxicities associated with the available Protease Inhibitors (PIs), has led to the adoption of EFV as a recommended component of highly active ART regimens (HAART) in the treatment of therapy-naïve infected patient. The sponsor, Mylan Pharmaceuticals Inc. has submitted an application for marketing approval of efavirenz EFV dosed at 400 mg once daily (qd) (b) (4) that provides antiretroviral efficacy with less CNS toxicity compared to EFV dosed at 600 mg qd (b) (4) in ART-naïve participant over 48 weeks. EFV is an oral tablet available in this study as 400 and 600 mg tablets. The sponsor reports that the study regimen of reduced dose of EFV(400 mg qd) was non-inferior to the standard (600 mg qd) EFV.

Inspections were requested for the study Protocol ENCORE1 for treatment-naïve HIV-1 infected adult subjects. The study protocol is outlined below:

Protocol ENCORE1: A randomized, double-blind, placebo controlled, clinical trial to compare the safety and efficacy of reduced dose efavirenz (EFV) with standard dose EFV plus 2 N (t) RT) in treatment of antiretroviral-naïve HIV-1-infected individuals over 96 weeks.

The primary objective of this study was to determine whether a targeted dose reduction of EFV provides an optimal balance of safety, efficacy, and tolerability across a range of population settings. The primary endpoint was the proportion of participants with plasma HIV RNA < 200 copies/mL (lower level of detection, LLD=50 copies/m/L).

This protocol was an international, multicenter, randomized, double-blind, placebo-controlled, 96 week non-inferiority trial of 600 mg once daily (qd) versus 400 mg qd of EFV administered with a 2N(t)RT1 backbone in ART-naïve HIV-infected individuals reaching criteria for initiation of combination ART. Approximately 600 subjects were enrolled, and all at foreign sites. Subjects were randomized in a 1:1 ratio and received efavirenz as follows:

- Group 1: EFV 600 mg + tenofovir (TDF) (300 mg qd/emtricitabine (FTC) (200 mg qd)
- Group 2: EFV 400 mg+TDF (300 mg qd)/FTC(200 mg qd)

The duration of the study for a given subject was 96 weeks including the extension phase. The primary endpoint was the proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 48.

According to the sponsor, no significant drug related safety concerns were identified. The results of the ENCORE1study demonstrated the feasibility of the dose reduction of EFV without a significant impact on efficacy based on virological and immunological endpoints and with a marginal enhancement in safety and tolerability.

The reasons for foreign inspection were, the relatively high rate of noncompliance at foreign sites, and the substantial amount of clinical trial experience with dose reduction of efavirenz at foreign sites.

The CDER review division team and OSI with input from statistics were involved in the selection process. The sites were selected principally due to relatively high patient accrual in the study and site specific protocol violations. The clinical site inspections were intended to help verify the data integrity.

Number of subjects: 630 randomized; 1:1 (315:315 to each arm)
Number of sites: 38
Participant countries: 13 ex-U.S.
First subject screened: September 5, 2011
Last subject observation/visit: March 14, 2014

Site Selection for Study Protocol ENCORE1

Site #1201 in Thailand (Dr. Phanuphank) and Site #2003 in South Africa (Dr. Orrell) had a relatively large number of subjects and a high response rate. Site #2101 in Singapore (Dr. Young) had a relatively large number of subjects. None of the sites had a history of previous inspection in our FDA database.

III. RESULTS (by site):

Name of CI, Site #, Address, Country if non-U.S. or City, State if U.S.	**Protocol # and # of Subjects**	**Inspection Date**	**Final Classification**
Praphan Phanuphak, M.D. Thai Red Cross AIDS Res. Ctr. 104 Ratchadamri Road Pathumwan, Bangkok, Thai Site #1201	ENCORE1 Subject: screened: 72 enrolled: 68	12/21-23/2016	Pending (preliminary classification NAI)
Catherine Orrell, M.D. University of Cape Town Anzio Rd., Observatory Cape Town, South Africa Site #2003	ENCORE1 Subjects screened: 81 enrolled: 64	12/5-9/2016	Pending (preliminary classification NAI)
Barnaby Young , M.D. Tan Tock Seng Hospital Infectious Disease Res. Ctr. Moulmein Road Singapore 308433 Site #2101	ENCORE1 Subjects screened: 48 enrolled: 40	12/5-7/2016	Pending (preliminary classification NAI)

Key to Compliance Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data are unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

NOTE: Site inspections focused on 100% review of informed consent documents, IRB, ethics committee correspondence, financial disclosures, training records, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, vital signs, subject source documents, including medical history records, drug accountability, and the use of concomitant medications. Source documents were compared to data listing for primary efficacy endpoints and adverse events reporting.

1. **Praphan aPhanuphak, M.D./Site #1210 / Study ENCORE1**
   Bangkok, Thailand

   There were 72 subjects screened, 4 subjects were reported as screen failures, and 68 subjects were enrolled in the study. Two subjects discontinued (1 death, and 1 moved away). Two subjects transferred from other sites, and 70 subjects completed the study.

   The medical records for 55 subjects were reviewed for informed consent and primary efficacy endpoints. Records were organized and legible. Medical records/source documents were compared to case report forms and data listings for primary efficacy endpoints and adverse event reporting. Minor transcription errors regarding vital signs for one subject were found. The audit revealed adequate adherence to the regulations and investigational plan. There were no objectionable conditions noted, and no Form FDA 483 was issued to Dr. Phanuphak.

   The data generated by this site appear acceptable. The inspection did not indicate serious deviations/findings that would impact the acceptability of the data submitted in support of the application.

2. **Catherine Orrell, M.D./ Site #2003/Study ENCORE1**
   Cape Town, South Africa

   There were 81 subjects screened, 17 subjects were reported as screen failures, 64 subjects enrolled in the study, nine subjects discontinued and the reasons were documented. 55 subjects completed the study. Of the nine subjects discontinued, the reason(s) were: five subjects withdrew consent, two died unrelated to study medication, one subject transferred to another site, and one subject went to prison. The field investigator reported that the primary endpoints were not derived at the site. No data integrity issues were found and no safety concerns were noted.

   The medical records for all subjects were reviewed. Record*s* were organized and legible. Medical records/source documents were compared to data listings for primary efficacy endpoint and adverse events reporting. No deficiencies were observed. The audit revealed adequate adherence to the regulations and investigational plan. No discrepancies were

found. There were no objectionable conditions noted and no Form FDA 483 was issued to Dr. Orrell.

Overall, the data generated at Dr. Orrell's site for ENCORE1 in support of clinical efficacy and safety is considered reliable and may be used in support of the pending application.

3. **Barnaby Young, M.D./ Site #2101/Study ENCORE 1**
Moulmein Road, Singapore 308433

There were 48 subjects screened, eight subjects were reported as screen failures, and 40 subjects were enrolled. There were no withdrawals/discontinuations or early terminations. All 40 subjects completed the study. The medical records for all subjects were reviewed.

The medical records/source documents were compared to case report form and data listings for primary efficacy endpoint and adverse event reporting. No deficiencies were noted. The inspection revealed adequate adherence to the regulations and investigational plan. There were no objectionable conditions noted, and no Form FDA-483 Inspectional Observations was issued. The field investigator reported that the medical records were organized and legible.

The data generated by this site appear acceptable. The inspection did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

{See appended electronic signature page}

Antoine El Hage, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
Team Leader and Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Enforcement
Office of Scientific Investigations

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/s/

ANTOINE N EL HAGE
01/09/2017

SUSAN D THOMPSON
01/09/2017

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: September 28, 2016

TO: Debra Birnkrant, M.D.
Director, Division of Antiviral Products (DAVP)
Office of Antimicrobial Products
Office of New Drugs (OND)

Dale Conner, Pharm.D.
Director (Acting)
Office of Bioequivalence (OB)
Office of Generic Drugs (OGD)

FROM: Gopa Biswas, Ph.D.
Pharmacologist
Division of New Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles Bonapace, Pharm. D.
Director
Division of New Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Review of EIR for For-Cause Inspection of Mylan Laboratory Ltd., Hyderabad, India.

Inspection Summary:

This was a FY2016 unannounced PDUFA PEPFAR and GDUFA For-Cause inspection. The inspection was conducted jointly by investigators from CDER/OSIS and FDA's India Office to investigate a complaint received from an informant with concerns regarding the bioanalytical operations of Mylan Laboratory, Clinical Research Center (CRC), Hyderabad, India. The allegations in the complaint included switching pivotal BE study drugs with R&D pilot BE study drugs and substituting plasma samples from pivotal BE studies with plasma samples from R&D pilot BE studies.

The inspection did not identify evidence to confirm the allegations in the complaint. The investigators confirmed that all pivotal BE study drugs were routed by Mylan's manufacturing site located at Sinnar, Nashik District, Maharashtra through the R&D site located at Bollaram, Hyderabad before being sent to CRC, Hyderabad for

distribution to CROs. However, the inspection did not uncover evidence for switching study drugs between pivotal BE study and R&D pilot BE studies or substituting plasma samples from pivotal BE studies with plasma samples from R&D pilot BE studies.

At the conclusion of the inspection, Form FDA 483 was not issued. The final classification for this inspection is No Action Indicated (NAI). Based on the inspectional outcome, we recommend that the data from the analytical portion of the bioequivalence studies audited during the inspection be accepted for further Agency review.

NDA 208255 (PEPFAR):

Study Number: C15275
Study Title: "A randomized, open-label, balanced, two-treatment, two-period, two sequence, single-dose, crossover oral bioequivalence study of Test product Tenofovir disoproxil fumarate, Lamivudine and Efavirenz film coated tablets 300 mg / 300 mg/ 400 mg of Mylan Laboratories Limited, India with Reference product (R= R1 + R2 + R3) (R1: VIREAD® Tablets (Tenofovir disoproxil fumarate) 300 mg manufactured and distributed by Gilead Sciences, Inc. Foster City, CA 94404,R2: EPIVIR® Tablets (Lamivudine) 300 mg Manufactured by GlaxoSmithKline Research Triangle Park, NC 27709, R3: Two tablets of Efamat (Efavirenz) 200 mg manufactured by Mylan Laboratories Ltd, India), in normal healthy adult human subjects under fasting conditions."
Dates of Study Conduct: December 21, 2015 - January 04, 2016 (Efavirenze)
December 21-30, 2015 (Tenofovir and Lamivudine)

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[redacted] (b) (6)

Final Classification:

NAI: Mylan Laboratory Ltd., Hyderabad, India
FEI: 3006355432

DARRTS CC:
OTS/OSIS/Kassim/Kadavil/Fenty-Stewart/Nkah/Miller/
Johnson/Taylor/Mirza
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDBE/Cho/Skelly/Choi
CDER/OND/OAP/DAVP/Birnkrant
CDER/OGD/OB/Conner

Draft: GB 09/20/2016
Edit: CB 09/27/2016

#s: 7179 (NDA 208255) [redacted] (b) (6)

O: BE\EIRCOVER\Mylan Laboratory Ltd.
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/ Analytical Site/ Mylan Laboratory Ltd., Hyderabad, India

FACTS: 11656094

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/s/

GOPA BISWAS
09/29/2016

WILLIAM H TAYLOR
09/29/2016

CHARLES R BONAPACE
09/30/2016

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: September 20, 2016

TO: Debra Birnkrant, M.D.
Director, Division of Antiviral Products (DAVP)
Office of Antimicrobial Products
Office of New Drugs (OND)

Dale Conner, Pharm.D.
Director (Acting)
Office of Bioequivalence (OB)
Office of Generic Drugs (OGD)

FROM: Amanda Lewin, Ph.D.
Pharmacologist
Division of New Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Directory
Division of New Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Surveillance Inspection of [redacted] (b) (4) covering NDA 208255, [redacted] (b) (4) [redacted] (b) (4)

Summary:

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of the clinical portion of bioequivalence studies [redacted] (b) (4) C15275 at [redacted] (b) (6) [redacted] (b) (4). No significant deficiencies were observed and no Form FDA 483 was issued. The final classification for [redacted] (b) (4) is no action indicated (NAI). After review of the inspectional findings, I recommend that the data from Studies [redacted] (b) (4) C15275 be accepted for further agency review.

NDA 208255

Study Number: C15275

Study Title: "A randomized, open-label, balanced, two-treatment, two-period, two-sequence, single-dose, crossover oral bioequivalence study of Test product Tenofovir disoproxil fumarate, Lamivudine and Efavirenz film-coated tablets 300 mg/300 mg/400 mg of Mylan Laboratories Limited, India with Reference product (R= R1 + R2 + R3) (R1: VIREAD® Tablets (Tenofovir disoproxil fumarate) 300 mg manufactured and distributed by Gilead Sciences, Inc. Foster City, CA 94404, R2: EPIVIR® Tablets (Lamivudine) 300 mg manufactured by GlaxoSmithKline, Research Triangle Park, NC 27709, R3: Two tablets of Efamat (Efavirenz) 200 mg manufactured by Mylan Laboratories Ltd., India), in normal healthy adult human subjects under fasting conditions"

Study Dates: 11/20/2015 to 12/21/2015

(b) (4)

(b) (4)

The inspection was conducted by ORA Investigator Scott B. Laufenberg at (b) (4)
(b) (4) The inspection included a thorough review and examination of firm history, clinical study performance, informed consent process, ethics committee approvals and correspondence, inclusion/exclusion criteria adherence, test article accountability/dispensation/storage, adverse events, concomitant medications, processing and handling of biological samples collected during the studies, equipment calibration, employee training, computer controls, and review of on-going study activities. Reserve samples collected for (b) (4)
C15275 were shipped to CDER-DPA in St. Louis, MO. (b) (4)

No significant deficiencies were observed during the inspection and no Form FDA 483 was issued at the conclusion of the inspection.

Conclusion:

After evaluation of the EIR and inspectional findings, the data from the audited studies were found to be reliable. Therefore, I recommend that the data from the clinical portion of bioequivalence studies [redacted] C15275 be accepted for further agency review.

Amanda Lewin, Ph.D.
Division of New Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

Final Classification:
NAI – [redacted]

CC:
OTS/OSIS/Kassim/ Kadavil/Fenty-Stewart/Nkah/Miller/Johnson
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Lewin
OTS/OSIS/DGDBE/Cho/Skelly/Choi/Au
CDER/OGD/OB/Conner
CDER/OND/OAP/DVAP/Birnkrant
ORA/Laufenberg

Draft: AEL 9/14/2016
Edit: GB 9/15/2016 AD 09/20/2016

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/ Clinical Site/ [redacted] NDA 208255_Tenofovir Disoproxil Fumarate, Lamivudine and Efavirenz Film-Coated Tablets/ Review (EIR Cover)

BE File #s: BE7179 (NDA 208255) [redacted]

FACTS: [redacted]

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/s/

AMANDA E LEWIN
09/20/2016

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ARINDAM DASGUPTA
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