APPLICATION NUMBER:

210649Orig1s000

OTHER REVIEW(S)
Clinical Labeling and Regulatory Review

<table>
<thead>
<tr>
<th>Date</th>
<th>March 8, 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>From</td>
<td>Monica Zeballos, Pharm.D.</td>
</tr>
<tr>
<td>Program Coordinator</td>
<td>Division of Antiviral Products (DAVP)</td>
</tr>
<tr>
<td>Through</td>
<td>Jeffrey Murray, M.D., M.P.H., Deputy Director, DAVP</td>
</tr>
<tr>
<td>NDA Number</td>
<td>NDA 210649</td>
</tr>
<tr>
<td>Original Regulatory Action and Date</td>
<td>PEPFAR, CR (Complete Response) on 13March2018 and 12Sept2018</td>
</tr>
<tr>
<td>Applicant</td>
<td>Macleods Pharmaceuticals Limited (Macleods), India</td>
</tr>
<tr>
<td>U.S. Agent</td>
<td>AB Pharmaceuticals, LLC; POC: Andrej Gasperlin, President</td>
</tr>
<tr>
<td>Letter Date</td>
<td>Sept 16, 2018</td>
</tr>
<tr>
<td>Stamp Date</td>
<td>Sept 17, 2018</td>
</tr>
<tr>
<td>Goal Date</td>
<td>Sunday, March 17, 2019, but will take action March 15, 2019</td>
</tr>
<tr>
<td>Established Name</td>
<td>Efavirenz (EFV), Lamivudine (3TC) and Tenofovir Disoproxil Fumarate (TDF)</td>
</tr>
<tr>
<td>Proprietary Name</td>
<td>None</td>
</tr>
<tr>
<td>Dosage Form/Strength</td>
<td>Tablets, 400 mg/300 mg/300 mg</td>
</tr>
<tr>
<td>Subject</td>
<td>Class 2 Resubmission to the 12Sept2018 CR, Eligible Only for Final Approval</td>
</tr>
</tbody>
</table>

Materials Reviewed and Labeling Consultant Reviews

1. Electronic Resubmissions (SDN01 dated/received 26June2017 & SDN09 dated 16Sept2018, received 17Sept2018 in DARRTS) and NDA-210649-ORIG-1-RESUB-9 received 17Sept2018 in Panorama, which did not contain any updated labeling
2. Current U.S. labeling for the reference products: a) NDA 21360/S044 SUSTIVA (efavirenz) tablets, 600 mg approved on 10Oct2017, b) NDA 20564/S038 EPIVIR (lamivudine) tablets, 300 mg approved on 27April2018, and c) NDA 21356/S057 VIREAD (tenofovir disoproxil fumarate) tablets, 300 mg approved on 11Dec2018
3. OSE/DMEPAa Review of the PI/PPI & Container Labeling dated 15Feb2019
4. OPQb Labeling Recommendations for the PI & Container Labeling dated 15Feb2019
5. OMP/OPDPc Review of the PI and Container Labeling dated 12March2019
6. Combined OMP/OPDPc and OMP/DMPPd Review of the PPI dated 13March2019

Recommended Approval

*aOffice of Surveillance and Epidemiology/Division of Medication Error Prevention and Analysis
bOffice of Pharmaceutical Quality
I. Background

On 03 July 2017, the Division issued an unacceptable (UN) for filing letter to Macleods’s original 505(b)(2) NDA 210649 submitted on 26 June 2017 for use under PEPFAR (President’s Emergency Plan for AIDS Relief) because FDA did not receive the appropriate user fee payment nor granted a waiver for this NDA. On 14 Sept 2017, the application user fee was waived, which means the Division accepted this NDA for filing on 14 Sept 2017 after the application was originally UN for filing.

This NDA was never tentatively approved and is now only eligible for final approval because the period of patent/exclusivity protection for the reference products (listed drugs) that have an HIV-1 treatment indication and that this NDA is relying upon has now expired. On March 14, 2019, Nisha Shah of the Office of Regulatory Policy (ORP) issued an exclusivity memo to support the approval of NDA 210649 for the indication of HIV-1 treatment. VIREAD (1 of 3 listed drugs) still has an unexpired exclusivity for the treatment of chronic hepatitis B virus (HBV) in pediatric patients, but NDA 210649 is not seeking approval for the treatment of chronic HBV. Therefore, ORP concluded that VIREAD’s unexpired exclusivity does not block the approval of NDA 210649.

In order for FDA to accept for review this fixed combination NDA, which incorporated reduced efavirenz 400 mg (EFV400), Macleods met two requirements: 1) obtained a right of reference for the clinical trial data (ENCORE1), which established the safety and efficacy of EFV400 and was submitted under pre-IND 128512 and 2) established comparability between the U.S. listed drug SUSTIVA and the efavirenz formulation used in ENCORE1, Mylan’s Efavirenz tablet, 200 mg (EFAMAT). Macleods conducted a relative bioavailability study comparing its EFV400 tablet with EFAMAT.

This NDA was issued two CR actions on 13 March 2018 and 12 Sept 2018, both due to inspectional issues with the Macleods Pharmaceutical Limited, Baddi (FEI # 3007517881) site. On 16 Sept 2018, Macleods submitted a class 2 resubmission to the 12 Sept 2018 CR and based on Macleods’s 11 Oct 2018 responses via email, the Division communicated that it had no objection to Macleods’s proposal to withdraw the original Macleods Pharmaceutical Limited, Baddi (FEI # 3007517881) site as a commercial tablet manufacturing facility from the NDA and replace it with Macleods Pharmaceutical Limited, Daman (FEI # 3006363714).

Because NDA 210649 is eligible for final approval, Macleods complied with all the requirements for approval such as participation in the Antiretroviral Pregnancy Registry and labeling that comply with all U.S. regulations (uniqueness of drug product appearance per 21 CFR 206; child-resistant packaging per 16 CFR 1700, etc.). In addition, OND’s 505(b)(2) Clearance Committee cleared NDA 210649 for approval on 19 Feb 2019.

At the time of initial submission, NDA 210649 triggered PREA (Pediatric Research Equity Act) as a new active ingredient (new combination product). However, because a similar equivalent (SYMFI LO under NDA 208255) was approved during the review of NDA 210649, the Pediatric Review Committee (PeRC) determined that PREA no longer applied to NDA 210649. In addition, NDA 210649 did not have to be submitted as an
ANDA because a complete NDA 210649 was submitted to FDA prior to the approval of SYMFI LO.

II. Labeling Review

All sections of the Prescribing Information (PI) and Patient Package Insert (PPI) for this 3-drug fixed combination product were reviewed, updated, and compared to the latest approved U.S. labeling for SUSTIVA, EPIVIR, and VIREAD. In addition, language from the clinical trial ENCORE1 captured in the PI of SYMFI LO was used. Labeling recommendations for the PI from consulting offices (OPQ, OSE/DMEPA) are included in the annotated PI sent to Macleods on 08March2019 and 15March2019 and additional recommendations from other consulting offices (OMP/OPDP and OMP/DMPP) are included in the clean version of the PPI sent to Macleods on 13March2019. The content and format of the PPI were completely reformatted to be consistent with the PI and current practices. Both annotated PI and clean PPIs (2 versions) are attached at the end of this memo. Labeling recommendations for the container labels were addressed separately.

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

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

2. Revised the proposed INDICATION AND USAGE section as follows:

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients weighing at least 35 kg.

3. Added the following to DOSAGE AND ADMINISTRATION section:

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

Prior to or when initiating efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, test patients for hepatitis B virus (HBV) infection [see Warnings and Precautions (5.1)].

Prior to initiation and during treatment with efavirenz, lamivudine and tenofovir disoproxil fumarate tablets, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus. [see Warnings and Precautions (5.3)].

2.2 Recommended Dosage

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is a fixed-dose combination product containing 400 mg of efavirenz (EFV), 300 mg of lamivudine (3TC), and 300 mg of tenofovir disoproxil fumarate (TDF). The recommended dosage regimen of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets in adults and pediatric
patients weighing at least 35 kg (77 lb) is one tablet once daily orally. Efavirenz, lamivudine and tenofovir disoproxil fumarate 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 (5.5) and Adverse Reactions (6.1)].

2.3 Not Recommended in Renal Impairment

Because efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is a fixed-dose combination product and cannot be dose adjusted, it is not recommended for patients requiring dosage adjustment, patients with creatinine clearance less than 50 mL per min, or patients with end-stage renal disease (ESRD) requiring hemodialysis [see Use in Specific Populations (8.6)].

2.4 Not Recommended in Moderate to Severe Hepatic Impairment

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C) [see Warnings and Precautions (5.8) and Use in Specific Populations (8.7)].

4. Revised/added the following to the CONTRAINDICATIONS section:

4.1 Hypersensitivity

Efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is contraindicated in patients:

- with prior hypersensitivity reaction (e.g., Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to efavirenz [see Warnings and Precautions (5.7)], lamivudine, or tenofovir disoproxil fumarate.
- when coadministered with elbasvir and grazoprevir [see Warnings and Precautions (5.2) and Drug Interactions (7.5)].

5. The bioequivalence of efavirenz, lamivudine and tenofovir disoproxil fumarate tablets was assessed in a study under fasted conditions only; therefore, this fixed combination product should be taken on an empty stomach, preferable at bedtime. Dosing at bedtime may improve the tolerability of nervous system symptoms caused by EFV.

6. Important information for the individual components (SUSTIVA, EPIVIR, and VIREAD) relevant to the use of this combination product was added to the WARNINGS AND PRECAUTIONS (5), ADVERSE REACTIONS (6), DRUG INTERACTIONS (7), USE IN SPECIFIC POPULATIONS (8), DESCRIPTION (11), CLINICAL PHARMACOLOGY (12), HOW SUPPLIED/STORAGE AND HANDLING (16), and PATIENT COUNSELING INFORMATION (17) sections as follows:

- Subsections 5.1, 5.2, 5.6, & 5.8: Added updated information regarding Severe Acute Exacerbation of Hepatitis B in Patients with HBV Infection for 3TC and TDF, Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions, Embryo-Fetal Toxicity for EFV, and Hepatotoxicity for EFV.
Subsection 6.1: Updated adverse reaction information for Trial 903 in treatment-naïve HIV-1 infected adult subjects that contained the 3 components and added pancreatitis information in pediatric subjects for 3TC

Section 7: Added information regarding Not Recommended with Other Antiretroviral Medications, Established and Other Significant Drug Interactions, and Drugs Inhibiting Organic Cation Transporters and Sorbitol, both for 3TC

Subsection 8.1 & 8.2: Added information according to the Pregnancy and Lactation Labeling Rule (PLLR) for EFV, 3TC, and TDF

Subsection 8.3: Added information regarding Females and Males of Reproductive Potential for the combination

Subsections 8.4, 8.6, & 8.7: Added use in pediatric patients and patients with renal and hepatic impairment

Section 11: Per OPQ’s labeling recommendations added revisions, including therapeutic category for all three components

Subsections 12. 2 & 12.3: Added pharmacodynamics information for EFV, updated pharmacokinetics information for 3TC and TDF, and drug interaction information for all three components

Subsection 12.4: Added updated Mechanism of Action information for EFV, Antiviral Activity in Cell Culture information for 3TC & TDF, and Resistance in Cell Culture information EFV, 3TC & TDF

Section 16: Per OPQ’s labeling recommendations changed storage statement based on demonstrated stability and added “child-resistant cap” for bottle of 30 and 90 tablets

Section 17: Reformatted and added all information to be consistent with the rest of the PI, including information about Pregnancy Exposure Registry, Missed Dose, and Storage

7. Information from the ENCORE1 clinical trial for EFV400 relevant to the use of this combination was added to the HIGHLIGHTS, WARNINGS AND PRECAUTIONS (5), ADVERSE REACTIONS (6), and CLINICAL STUDIES (14) sections as follows:

- HIGHLIGHTS: Added most common adverse reactions (based on the ENCORE1 trial only under the Adverse Reactions heading
- Subsections 5.4, 5.5, & 5.7: Added information regarding Psychiatric Symptoms, Nervous System Symptoms, and Skin and Systemic Hypersensitivity Reaction
- Subsections 6.2: Added adverse reaction information supported by clinical trial experience in treatment-naïve HIV-1 infected adult subjects
- Subsection 14.1: Added trial information, which evaluated the comparability of 400 mg of EFV in a triple drug regimen to a 600 mg dose of EFV in a triple drug regimen

III. Recommended Regulatory Action

The proposed PI and PPI were reviewed and should allow for the safe and effective use of this 3-drug fixed combination product. Macleods has adequately responded to the Division’s labeling revisions conveyed on 08March2019, 13March2019, and 15March2019, via email correspondence; therefore, an approval action is warranted.

Monica Zeballos, Pharm.D.
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/

MONICA I ZEBALLOS
03/15/2019 01:28:54 PM

JEFFREY S MURRAY
03/15/2019 02:08:19 PM
PATIENT LABELING REVIEW

Date: March 13, 2019

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)

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

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

Drug Name (established name): efavirenz, lamivudine and tenofovir disoproxil fumarate
Dosage Form and Route: tablets, for oral use
Application Type/Number: NDA 210649
Applicant: Macleods Pharmaceuticals Limited
1 INTRODUCTION

On September 17, 2018, Macleods Pharmaceuticals Limited re-submitted for the Agency’s review a 505(b)(2) New Drug Application (NDA) 210649 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 Complete Response Letter issued on September 12, 2018. The Reference Listed Drugs (RLDs) are SUSTIVA (efavirenz) tablets NDA 021360, EPIVIR (lamivudine) tablets NDA 020564 and VIREAD (tenofovir disoproxil fumarate) tablets NDA 021356. The proposed indication for efavirenz, lamivudine and tenofovir disoproxil fumarate tablets is as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients weighing at least 35 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 March 7, 2019, 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 September 17, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 7, 2019.
- Draft efavirenz, lamivudine and tenofovir disoproxil fumarate tablets Prescribing Information (PI) received on September 17, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 7, 2019.
- Approved SYMFI LO (efavirenz, lamivudine and tenofovir disoproxil fumarate) tablets comparator labeling dated February 5, 2018.
- Approved SUSTIVA (efavirenz) tablets comparator labeling dated October 10, 2017.
- Approved EPIVIR (lamivudine) tablets comparator labeling dated April 27, 2018.
- Approved VIREAD (tenofovir disoproxil fumarate) tablets comparator labeling dated December 11, 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. (Reference: 4403137)
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.
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/

RUTH I LIDOSHORE
03/13/2019 12:40:38 PM

WENDY R LUBARSKY
03/13/2019 12:57:37 PM

BARBARA A FULLER
03/13/2019 01:08:40 PM

LASHAWN M GRIFFITHS
03/13/2019 01:15:55 PM
In response to DAVP consult request dated March 6, 2019, 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. On September 17, 2018, Macleods Pharmaceuticals Limited re-submitted for the Agency’s review a 505(b)(2) New Drug Application (NDA) 210649 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 Complete Response Letter issued on September 12, 2018. The Reference Listed Drugs (RLDs) are SUSTIVA (efavirenz) tablets NDA 021360, EPIVIR (lamivudine) tablets NDA 020564 and VIREAD (tenofovir disoproxil fumarate) tablets NDA 021356.

**PI and PPI:** OPDP’s comments on the proposed labeling are based on the draft PI and PPI received by electronic mail from DAVP (Monica Zeballos) on March 7, 2019, and one comment is provided below, in Section 2.2.

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

**Carton and Container Labeling:** OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DAVP (Monica Zeballos) on March 7, 2019, 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.
1.14.1.1 Draft Carton & Container Labels

The draft container labels for Efavirenz, Lamivudine and Tenofovir disoproxil fumarate Tablets 400 mg/300 mg/300 mg are provided under this section

- 30s count bottle pack
- 90s count bottle pack
- 180s count bottle pack
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/

WENDY R LUBARSKY
03/12/2019 12:41:21 PM
<table>
<thead>
<tr>
<th><strong>LABEL AND LABELING REVIEW</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Division of Medication Error Prevention and Analysis (DMEPA)</td>
</tr>
<tr>
<td>Office of Medication Error Prevention and Risk Management (OMEPRM)</td>
</tr>
<tr>
<td>Office of Surveillance and Epidemiology (OSE)</td>
</tr>
<tr>
<td>Center for Drug Evaluation and Research (CDER)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th><strong>Date of This Review:</strong></th>
<th>February 15, 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Requesting Office or Division:</strong></td>
<td>Division of Antiviral Products (DAVP)</td>
</tr>
<tr>
<td><strong>Application Type and Number:</strong></td>
<td>NDA 210649</td>
</tr>
<tr>
<td><strong>Product Name and Strength:</strong></td>
<td>Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate Tablets, 400 mg/300 mg/300 mg</td>
</tr>
<tr>
<td><strong>Product Type:</strong></td>
<td>Multi-Ingredient Product</td>
</tr>
<tr>
<td><strong>Rx or OTC:</strong></td>
<td>Prescription (Rx)</td>
</tr>
<tr>
<td><strong>Applicant/Sponsor Name:</strong></td>
<td>Macleods Pharmaceuticals LTD</td>
</tr>
<tr>
<td><strong>FDA Received Date:</strong></td>
<td>June 26, 2017 and September 17, 2018</td>
</tr>
<tr>
<td><strong>OSE RCM #:</strong></td>
<td>2018-2261</td>
</tr>
<tr>
<td><strong>DMEPA Safety Evaluator:</strong></td>
<td>Valerie S. Wilson, PharmD</td>
</tr>
<tr>
<td><strong>DMEPA Team Leader:</strong></td>
<td>Sevan Kolejian, PharmD, MBA</td>
</tr>
</tbody>
</table>

Reference ID: 4391877
1 REASON FOR REVIEW
As part of the approval process for Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate Tablets, 400 mg/300 mg/300 mg, the Division of Antiviral Products (DAVP) requested that we review the proposed labels and labeling for areas that may lead to medication errors.

2 REGULATORY HISTORY
Macleods Pharmaceutical LTD submitted NDA 210649 on June 26, 2017 to seek tentative approval under the President’s Emergency Plan for AIDS Relief (PEPFAR) program. However, the application received a complete response (CR) on March 13, 2018 and again on September 12, 2018 due to issues identified during a manufacturing facility inspection.a,b On September 17, 2018, Macleods submitted a response to the Agency’s CR letter to address the deficiencies identified by the Agency.

3 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>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section for Methods and Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Information/Prescribing Information</td>
<td>A</td>
</tr>
<tr>
<td>Previous DMEPA Reviews</td>
<td>B (N/A)</td>
</tr>
<tr>
<td>Human Factors Study</td>
<td>C (N/A)</td>
</tr>
<tr>
<td>ISMP Newsletters</td>
<td>D (N/A)</td>
</tr>
<tr>
<td>FDA Adverse Event Reporting System (FAERS)*</td>
<td>E (N/A)</td>
</tr>
<tr>
<td>Other</td>
<td>F (N/A)</td>
</tr>
<tr>
<td>Labels and Labeling</td>
<td>G</td>
</tr>
</tbody>
</table>

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 the identified medication error issues with the submitted prescribing information and container labels, DMEPA’s rationale for concern, and the proposed recommendation to minimize the risk for medication error.

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

<table>
<thead>
<tr>
<th>Prescribing Information</th>
<th>IDENTIFIED ISSUE</th>
<th>RATIONALE FOR CONCERN</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full Prescribing Information</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>Additional storage information is included in the Patient Information that is not included in Section 16 of the Full Prescribing Information (i.e. Keep efavirenz, lamivudine and tenofovir disoproxil fumarate tablets in the original container; Keep the bottle tightly closed; and Keep efavirenz, lamivudine and tenofovir disoproxil fumarate tablets and all medicines out of the reach of children).</td>
<td>Lack of consistency across the label and labeling could result in improper storage of the medication. Improper storage could result in administration of deteriorated drug. We confirmed with our Office of Pharmaceutical Quality colleagues that Section 16 and the container label should include the additional storage information included in the Patient Information.</td>
<td>For consistency and to minimize administration of deteriorated drug risk, we recommend Section 16 be revised to include the following storage recommendations: Store in original keep bottle tightly closed, and protect from moisture. Do not remove desiccant.</td>
</tr>
</tbody>
</table>
Table 3: Identified Issues and Recommendations for Macleods Pharmaceutical LTD (entire table to be conveyed to Applicant)

<table>
<thead>
<tr>
<th>Container Labels, Carton Labeling, and Packaging</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IDENTIFIED ISSUE</strong></td>
</tr>
<tr>
<td><strong>Container Labels</strong></td>
</tr>
<tr>
<td>1.</td>
</tr>
<tr>
<td>2.</td>
</tr>
<tr>
<td>3.</td>
</tr>
</tbody>
</table>

Reference ID: 4391877
4. Additional storage information is included in the labeling that is not included on the container label (i.e. *Keep efavirenz, lamivudine and tenofovir disoproxil*).

Improper storage could result in administration of deteriorated drug. We confirmed with our Office of Pharmaceutical Quality colleagues that the container label should

To minimize the risk of administration of deteriorated drug, we recommend you include the following storage recommendations on the container label:

- Expiration date on the drug package label include a year, month, and non-zero day. We recommend that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. We recommend that a hyphen or a space be used to separate the portions of the expiration date. See Draft Guidance: Product Identifiers Under the Drug Supply Chain Security Act-Questions and Answers, September 2018 (lines 277-283), for further insight into FDAs current thinking (found at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf).
fumarate tablets in the original container; Keep the bottle tightly closed; and Keep efavirenz, lamivudine and tenofovir disoproxil fumarate tablets out of the reach of children.

include additional storage information.

Store in original container, keep bottle tightly closed, and protect from moisture. Do not remove desiccant.
Keep out of reach of children.

5 CONCLUSION

Our evaluation of the proposed prescribing information, patient information, and container labels 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.
Table 4 presents relevant product information for Efavirenz, Lamivudine, and Tenofovir disoproxil fumarate Tablets received on June 26, 2017 from Macleods Pharmaceuticals LTD.

<table>
<thead>
<tr>
<th>Table 4. Relevant Product Information for Efavirenz, Lamivudine, and Tenofovir disoproxil fumarate Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Approval Date</strong></td>
</tr>
<tr>
<td><strong>Active Ingredient</strong></td>
</tr>
<tr>
<td><strong>Indication</strong></td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
</tr>
<tr>
<td><strong>Dosage Form</strong></td>
</tr>
<tr>
<td><strong>Strength</strong></td>
</tr>
<tr>
<td><strong>Dose and Frequency</strong></td>
</tr>
<tr>
<td><strong>How Supplied</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Storage</strong></td>
</tr>
<tr>
<td><strong>Container Closure</strong></td>
</tr>
</tbody>
</table>
APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,\(^c\) along with postmarket medication error data, we reviewed the following Efavirenz, Lamivudine, and Tenofovir disoproxil fumarate Tablets labels and labeling submitted by Macleods Pharmaceuticals LTD.

- Container label received on June 26, 2017
- Prescribing Information and Patient Information received on June 26, 2017 available at: \(\text{\textbackslash c\textbackslash dsesub1\textbackslash evsprod\nda210649\0000\m1\us\1-14-labeling\1-14-1-draft-labeling\1-14-1-3-draft-labeling-text\insert-labeling-text-pdf.pdf}\)

G.2 Label Images

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/

------------------------------------------------------------

VALERIE S WILSON  
02/15/2019 01:37:59 PM

SEVAN H KOLEJIAN  
02/15/2019 01:40:46 PM

Reference ID: 4391877
DATE: 11/21/2017

TO: Division of Antiviral Products
    Office of Antimicrobial Products

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
      Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Recommendation to accept data without an on-site inspection

RE: NDA 210649

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Inspection Sites

<table>
<thead>
<tr>
<th>Facility Type</th>
<th>Facility Name</th>
<th>Facility Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Macleods Pharmaceuticals, Ltd.</td>
<td>R and D-II, Plot No. 95, Road No. 16, Opposite Suncity Hotel, MIDC Industrial Estate, Andheri – (East), Mumbai, Maharashtra, India</td>
</tr>
<tr>
<td>Analytical</td>
<td>Macleods Pharmaceuticals, Ltd.</td>
<td>BE Dept., G-2, Mahakali Caves Road, Shanti Nagar, Andheri – (East), Mumbai, Maharashtra, India</td>
</tr>
</tbody>
</table>
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHILA S NKAH
11/21/2017