CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208351Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA #	208351
Product Name:	Emtricitabine, rilpivirine and tenofovir alafenamide Tablets 200 mg/25 mg/25 mg
PMC #1 Description:	Setting of final dissolution acceptance criterion for rilpivirine using the approved dissolution method

PMC Schedule Milestones:	Final Protocol Submission:	--
	Study/Trial Completion:	16 months after the action date
	Final Report Submission:	18 months after the action date
	Other:	--

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

   ☐ Need for drug (unmet need/life-threatening condition)
   ☐ Long-term data needed (e.g., stability data)
   ☐ Only feasible to conduct post-approval
   ☐ Improvements to methods
   ☐ Theoretical concern
   ☐ Manufacturing process analysis
   ☒ Other

   During the review of the NDA submission, it was determined that the Applicant's proposed dissolution acceptance criterion was not appropriate for the evaluation of the dissolution of the rilpivirine component of the proposed FDC drug product. Due to the PDUFA timeline of this PEPFAR NDA, it is not possible for the Applicant to accumulate dissolution data from additional commercial batches to support the proposed acceptance criterion. Instead, the Division of Biopharmaceutics is proposing an interim dissolution acceptance criterion that can be in place till the Applicant collects additional dissolution data and implements the final agreed upon dissolution acceptance criterion that is adequate for the evaluation of the dissolution of the rilpivirine component the proposed FDC product.

2. Describe the particular review issue and the goal of the study.

The following proposed dissolution method was found acceptable for rilpivirine (RPV) component:

	Speed	Volume	Medium
USP 2 (paddle)	75 rpm	1000 mL	0.5% Polysorbate 20 in 0.01 N HCl, pH 2 @37.0± 0.5° C

The dissolution data did not support the proposed acceptance criterion of Q = (b)(4)% at (b)(4) minutes, for rilpivirine. The provided dissolution data supported a dissolution acceptance criterion of Q=(b)(4)% at 30 minutes for rilpivirine. The FDA recommended that the Applicant revise the acceptance criterion to Q=(b)(4)% at 30 minutes for rilpivirine and to provide a revised drug product specification table and update the stability protocol accordingly. FDA also clarified that the dissolution testing may require stage 2 testing and occasionally stage 3 testing.

In a response dated 11/30/15, the Applicant did not agree with the FDA recommended acceptance criteria and proposed a revised acceptance criterion of Q = (b)(4)% at 45 minutes for rilpivirine (RPV).

The Applicant justified the proposed revised acceptance criterion [Q = (b)(4)% at 45 minutes] for rilpivirine (b)(4) The Applicant also stated that the Agency's proposed Q = (b)(4)% at the 30 minute time point would lead to a rate of Stage 2 testing at batch release of (b)(4)% (b)(4) total clinical batches) batches. The Applicant also claimed that the proposed revised acceptance criterion (45 minute time point) would (b)(4) (b)(4) (b)(4) (b)(4).

A T-con between FDA and the Applicant was held on 12/3/15 to discuss the FDA recommended and the Applicant proposed revised dissolution acceptance criterion. During the T-con, the Applicant argued that the product design is robust, dissolution is discriminating and tablet (b)(4) are (b)(4). In addition, the Applicant stated that the FDA recommended acceptance criterion [NLT (b)(4) % (Q) in 30 minutes] is tight and will lead to unnecessary stage 2 and 3 testing for a significant number of batches. The FDA and the Applicant could not agree on the final dissolution acceptance criterion for rilpivirine during the T-con.

In an email, dated 12/08/2015, the following FDA's Chemistry Manufacturing and Controls (CMC) Information Request, with two possible options, was sent to the Applicant.

The review team had further discussions to consider Q=(b)(4)% at the two possible regulatory time points for the rilpivirine dissolution test. FDA believes the data support the 30-minute time point rather than the 45-minute time point. We see two possible approaches to resolve this issue:

1. Agreement to use Q=(b)(4)% at the 30-min time point for the regulatory specification, or
2. Establishment of an interim specification with Q=(b)(4)% at the 45-min time point, with a Post-Marketing Commitment to compare results at the 30- and 45-min times after a sufficient amount of commercial manufacturing experience has been gained, upon which the final dissolution acceptance criterion for rilpivirine will be established.

In a response, dated 1/04/2016, the Applicant agreed to an interim rilpivirine dissolution specification of Q=(b)(4)% at 45 minutes and also agreed to a Post-Marketing Commitment to compare dissolution results from all commercial batches at the 30-minute and 45-minute time points. The Applicant also agreed to provide the requested information as a supplement 18 months post NDA approval.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon ?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☒ Dissolution Acceptance Criterion
- ☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☐ Other

Describe the agreed-upon study:

Under the PMC submission, the Applicant should provide the following:

A final Dissolution Report within eighteen (18) months from NDA's action date:

The Applicant should collect rilpivirine dissolution data at 30 and 45 minutes; n=12) from the registration batches under the stability program and from all new commercial batches using the approved dissolution method for rilpivirine (RPV). The Applicant should provide a statistical analysis of the obtained data and provide a prediction of the expected S2 and S3 testing rates. Based on these data, the Applicant should provide their proposal for the final dissolution acceptance criterion for the rilpivirine (RPV) component. The Applicant can submit the above stated information in a Prior Approval Supplement (PAS).

5. To be completed by ONDQA/OBP Manager:

- ☐ Does the study meet criteria for PMCs?
- ☐ Are the objectives clear from the description of the PMC?
- ☐ Has the applicant adequately justified the choice of schedule milestone dates?
- ☐ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs only)

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/s/

CHRISTIAN P YODER
03/01/2016

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 208351

Product Name: ODEFSEY® (emtricitabine, rilpivirine, tenofovir alafenamide) 200/25/25mg fixed-dose combination (FDC) tablet

PMR Description: Using data from agreed upon studies of the component products, conduct and submit an assessment of safety, pharmacokinetics, and antiviral activity of ODEFSEY in pediatric patients 6 years to less than 12 years of age or greater than 25kg.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	Submitted
	Study/Trial Completion:	09/2018
	Final Report Submission:	03/2019
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☒ Other

   The drug is ready for approval in adults and pediatric patients 12 years of age or older and the studies in younger pediatric patients are not complete.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of the deferred assessment is to determine the PK profiles of rilpivirine (RPV), emtricitabine (FTC) and tenofovir alafenamide (TAF) as component drugs of ODEFSEY (FTC/RPV/TAF) in pediatric patients 6 to less than 12 years of age and provide safety information in this pediatric age group. An

(b) (4)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☒ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

(b) (4)

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
X Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☐ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

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/s/

CHRISTIAN P YODER
03/01/2016

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:	February 23, 2016
Requesting Office or Division:	Division of Antiviral Products (DAVP)
Application Type and Number:	NDA 208351
Product Name and Strength:	Odefsey (emtricitabine, rilpivirine, and tenofovir alafenamide) Tablets 200 mg/25 mg/25 mg
Submission Date:	February 11, 2016 and February 22, 2016
Applicant/Sponsor Name:	Gilead Sciences, Inc
OSE RCM #:	2015-1505-1
DMEPA Primary Reviewer:	Mónica Calderón, PharmD, BCPS
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

Gilead Sciences, Inc has submitted the revised full prescribing information (FPI) and container labels (Appendix A) for Odefsey in response to recommendations we made during a previous label and labeling review.[1] Thus, the Division of Antiviral Products (DAVP) requested that we review the revised label and labeling to determine if it is acceptable from a medication error perspective.

2 CONCLUSIONS

[1] Calderon M. Label and Labeling Review for Odefsey (NDA 208351). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 Sept 23. 32 p. OSE RCM No.: 2015-1505.

The revised FPI and container label are acceptable from a medication error perspective. We have no further recommendations.

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/s/

MONICA M CALDERON
02/23/2016

BRENDA V BORDERS-HEMPHILL
02/24/2016

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

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

Memorandum

Date: **February 22, 2016**

To: **Christian Yoder, Regulatory Project Manager**
Division of Antiviral Products

From: Jessica Fox, PharmD, RAC, Regulatory Review Officer
Office of Prescription Drug Promotion

Subject: **NDA 208351 – ODEFSEY (emtricitabine, rilpivirine, and tenofovir alafenamide) tablets, for oral use**

As requested in the Division of Antiviral Products' (DAVP) consult dated July 28, 2015, the Office of Prescription Drug Promotion (OPDP) has reviewed the ODEFSEY prescribing information, patient labeling, and carton/container labeling.

OPDP reviewed the proposed substantially complete version of the prescribing information sent via email on February 4, 2016, and an updated version of the labeling obtained from SharePoint on February 18, 2016. OPDP's comments are included in the latter version of the labeling attached to this document.

The Division of Medical Policy Programs and OPDP provided a single, consolidated review of the patient labeling on February 18, 2016.

OPDP reviewed the carton/container labeling received in the EDR on January 29, 2016, and has no comments at this time.

Thank you for your consult. OPDP appreciates the opportunity to provide comments. If you have any questions, please contact Jessica Fox at (301) 796-5329 or Jessica.Fox@fda.hhs.gov.

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/s/

JESSICA M FOX
02/22/2016

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:	February 18, 2016
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:	Morgan Walker, PharmD, MBA Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Jessica Fox, PharmD, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	ODEFSEY (emtricitabine, rilpivirine, tenofovir alafenamide)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 208351
Applicant:	Gilead Sciences, Inc.

1 INTRODUCTION

On June 29, 2015, Gilead Sciences, Inc. submitted for the Agency's review a New Drug Application (NDA) 208351 for ODEFSEY (emtricitabine, rilpivirine, tenofovir alafenamide) tablets. The proposed indication for ODEFSEY (emtricitabine, rilpivirine, tenofovir alafenamide) is for use as a complete regimen for the treatment of HIV-1 infection in (b) (4) patients 12 years of age and older with no antiretroviral treatment history or who are virologically suppressed to replace (b) (4) (b) (4) antiretroviral (b) (4) regimen.

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 July 28, 2015, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ODEFSEY (emtricitabine, rilpivirine, tenofovir alafenamide) tablets.

2 MATERIAL REVIEWED

- Draft ODEFSEY (emtricitabine, rilpivirine, tenofovir alafenamide) tablets PPI received on June 29, 2015, and received by DMPP and OPDP on February 4, 2016.
- Draft ODEFSEY (emtricitabine, rilpivirine, tenofovir alafenamide) tablets Prescribing Information (PI) received on June 29, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 4, 2016.

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. In our review of the PPI the target reading level is at or below an 8th grade 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 have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- 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/

MORGAN A WALKER
02/18/2016

JESSICA M FOX
02/18/2016

BARBARA A FULLER
02/18/2016

LASHAWN M GRIFFITHS
02/18/2016

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 208351

Application Type: New NDA

Name of Drug/Dosage Form: emtricitabine/rilpivirine/tenofovir alafenamide fixed dose combination tablet 200/25/25 mg

Applicant: Gilead Sciences, Inc.

Receipt Date: July 1, 2015

Goal Date: March 1, 2016

1. Regulatory History and Applicant's Main Proposals

The new molecular entity, tenofovir alafenamide is currently under review in three new drug applications (NDA 207561, 208215, and 208351). New drug application 208351 for emtricitabine, rilpivirine, and tenofovir alafenamide FDC tablet for the treatment of HIV-1 infection in (b) (4) (b) (4) 12 years and older was received on July 1, 2015 from Gilead Sciences. The pivotal data to support the use of this product is from a bioequivalence study. The sponsor submitted the application with a tropical disease voucher giving it a priority review. Tenofovir alafenamide has not yet been approved so it is considered an NME and will be reviewed under PDUFA V's "The Program".

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by September 4, 2015 (choose a date within three weeks of the letter). The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

NO 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment: *The length of the HL section exceeds the one-half page requirement.A waiver of this requirement will be granted upon approval of the NDA.*

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

NO 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *The white space needs to be corrected as follows:*

****Space needs to be added under "Initial U.S. Approval"sectionand before the "Indication AND USAGE section.***

****Spacing underneath the following headings needs to be removed: DRUG INTERACTIONS, USE IN SPECIFIC POPULATIONS***

NO 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: *There are no references given in the "INDICATIONS AND USAGE" section for 2 paragraphs under "Limitations of Use:" and in the first bullet under "DRUG INTERACTIONS."*

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Selected Requirements of Prescribing Information

Boxed Warning (BW) in Highlights

YES 12. All text in the BW must be **bolded**.

Comment:

YES 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

YES 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

YES 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

YES 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

YES 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

NO 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment: *In 6.2 Post Marketing is written as 2 words, but in the FPI it is written as one word, Postmarketing*

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

NO 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*" or "[*see Warnings and Precautions (5.2)*]".

Comment: *Parentheses are missing around "8.4" in the reference in 12.3 Pediatric Patients "[See Use In Specific Populations 8.4]".*

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

YES 36. In the BW, all text should be **bolded**.

Comment:

YES 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

YES 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

YES

41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

CHRISTIAN P YODER
02/11/2016

KAREN D WINESTOCK
02/12/2016
This review was completed August12, 2015, but it was not placed in DARRTS for final sign-off

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: January 5, 2016

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

FROM: Gajendiran Mahadevan, Ph.D.
Staff Fellow
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
Division of New Drugs Bioequivalence Evaluation
Office of Study Integrity and Surveillance

and

Charles Bonapace, Pharm.D.
Director
Division of New Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

SUBJECT: Review of EIR Covering NON-RESPONSIVE NON-RESPONSIVE NDA 208351, Emtricitabine/Rilpivirine/Tenofovir Alafenamide (200/25/25 mg) FDC Tablets Sponsored by Gilead Sciences, Inc.

Inspection Summary: This is a FY 2015 PDUFA in vivo bioavailability study clinical site inspection. At the request of the Division of Antiviral Products (DAVP), the Office of Study Integrity and Surveillance (OSIS) arranged an inspection of the clinical portion of studies NON-RESPONSIVE GS-US-366-1159 (NDA 208351) at Seaview Jacksonville, LLC, Jacksonville, FL.

At the conclusion of the inspection, no significant issues were observed and no Form FDA 483 was issued. However, the data audit

revealed that NON-RESPONSIVE NON-RESPONSIVE NON-RESPONSIVE subject 1088 (study GS-US-366-1159) may have been taking prescription medication on the day of admission to the clinical site. After review of the establishment inspection report, I recommend that the clinical data from NON-RESPONSIVE GS-US-366-1159 be accepted for further Agency review. The final classification for this inspection is no action indicated (NAI).

Application Type & Number: NON-RESPONSIVE
Study #:
Study Title:

Dates of Study Conduct:

Application Type & Number: NDA 208351
Study #: GS-US-366-1159
Study Title: "A phase 1, randomized, open-label, single-dose, three-way, six-sequence, cross-over study to evaluate the bioequivalence of Emtricitabine, Rilpivirine and Tenofovir Alafenamide from a fixed-dose combination of Emtricitabine/Rilpivirine/Tenofovir Alafenamide (200/25/25 mg) relative to Elvitegravir/ Cobicistat/Emtricitabine/Tenofovir Alafenamide (150/150/200/10 mg) fixed-dose combination and Rilpivirine (25 mg)"

Dates of Study Conduct: October 21-December 26, 2014

Clinical Inspection:

The clinical site inspection was conducted by Traci Armand (ORA, FLA-DO) between October 26 and November 3, 2015 at **Seaview Jacksonville, LLC, Jacksonville, FL.** The inspection included a thorough examination of the protocol, protocol amendments, study records, informed consent forms, SOPs, IRB approvals, case report forms, and interviews/discussions with the firm's staff and management. At the conclusion of the inspection, no significant issues were observed and no Form FDA 483 was issued. However, the data audit revealed that NON-RESPONSIVE NON-RESPONSIVE subject 1088 (study GS-US-366-1159) may have been taking prescription medication on the day of admission to the clinical site.

NON-RESPONSIVE

Subject 1088 (Study GS-US-366-1159) – This subject had a confirmed intrauterine device (IUD) and was prescribed Bactrim DS tablets twice a day for three days on November 4, 2014 for a urinary tract infection. On November 6, 2014, the subject's response to question number 9a on the Admission Questionnaire, "Have you taken any prescription medication or over-the-counter medication including herbal products (such as St. John's Wort), antacids, and proton pump inhibitors (i.e., esomeprazole, dexlansoprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole) since your last visit?" was "No" (**Attachment-2**). It is likely that the subject was still on the prescription medication on the day of admission to the clinic and one day prior to the administration of the investigational drug products on November 7, 2014 (**Attachment-3**). Taking any prescription or over-the-counter medications would exclude the subject from

participation in the study per the "Exclusion Criteria" set by the sponsor (**Attachment-4**).

Recommendations:

- The DAVP medical reviewer should evaluate the impact of the NON-RESPONSIVE prescription medication for subject 1088.

- Following the evaluation of the inspectional findings and the EIR, the clinical data from NON-RESPONSIVE GS-US-366-1159 were found to be reliable. Therefore, I recommend that the data generated at **Seaview Jacksonville, Jacksonville, FL** be accepted for further Agency review.

Gajendiran Mahadevan, Ph.D.
DNDBE, OSIS

Final Classification:

NAI: Seaview Jacksonville, Jacksonville, FL
FEI#: 3011861600

E-mail CC:
OSIS/Kassim/Taylor/Fenty-Stewart/Nkha/Miller
OSIS/DGDBE/Haidar/Skelly/Choi
OSIS/DNDBE/Bonapace/Dasgupta/Cho/Mahadevan

CDER/OND/OAP/DAVP/Birnkrant/Hong/Yoder

ORA/FLA-DO/Sinninger/Armand NON-RESPONSIVE

Draft: GM 01/04/2016
Edit: AD 01/04/2016; CB 01/04/2016

OSIS File: BE NON-RESPONSIVE 6943; O:\BE\EIRCOVER 208351.emt.gil
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE inical
cksonville, Jacksonville, FL/ NON-RESPONSIVE NON-RESPONSIVE

ATTACHMENT-1

6 Page(s) has been Withheld in Full as NON-RESPONSIVE immediately following this page

ATTACHMENT-2

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ATTACHMENT-3

Listing 1: Disposition
Analysis Set: All Randomized

Subject ID	Treatment Sequence	First Dose Date	Last Dose Date [Day]	Safety Analysis Set	PK Analysis Set					Completed Study Drug?	Reason for Discontinuation from Study Drug	Completed Study?	Reason for Discontinuation from Study
					RPV	EVG	COBI	FTC	TAF				
9191-1079	CBA	07NOV2014	05DEC2014 [29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	
9191-1080	BAC	07NOV2014	05DEC2014 [29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	
9191-1081	ABC	07NOV2014	05DEC2014 [29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	
9191-1082	ABC	07NOV2014	05DEC2014 [29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	
9191-1083	CBA	07NOV2014	05DEC2014 [29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	
9191-1084	CAB	07NOV2014	05DEC2014 [29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	
9191-1085	BAC	07NOV2014	05DEC2014 [29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	
9191-1086	CBA	07NOV2014	05DEC2014 [29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	
9191-1087	BCA	07NOV2014	05DEC2014 [29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	
9191-1088	CAB	07NOV2014	05DEC2014 [29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	
9191-1089	CBA	07NOV2014	05DEC2014 [29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	
9191-1090	ACB	07NOV2014	05DEC2014 [29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	
9191-1091	CAB	07NOV2014	05DEC2014 [29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	

Note: Day is the number of days relative to the first dose in the first period. Study Day is relative to the first dose of that treatment.

Data Extracted: CRF data: 10APR2015
Source: ...\Version 2\Listings\l-disposit.sas, v9.2, 14APR2015: 9:16

ATTACHMENT-4

15. A normal 12-lead electrocardiogram (ECG) with normal PR and QTcF intervals, or one with abnormalities that were considered clinically insignificant by the investigator in consultation with the sponsor

16. Willing and able to comply with all study requirements.

7.3.2. Exclusion Criteria

Subjects with any of the following were not eligible for participation in the study:

1. Pregnant or lactating females.

2. Any serious or active medical or psychiatric illness which, in the opinion of the investigator, interfered with subject treatment, assessment, or compliance with the protocol. This included renal, cardiac, hematological, hepatic, pulmonary (eg, chronic asthma), endocrine (eg, diabetes), central nervous, gastrointestinal (eg, ulcer), vascular, or metabolic disorders (eg, thyroid disorders, adrenal disease), immunodeficiency disorders, active infections, or malignancies that were clinically significant or required treatment.

3. Previously participated in an investigational trial involving administration of any investigational compound within 30 days prior to the study dosing

4. Current alcohol or substance abuse judged by the investigator to potentially interfere with subject compliance and/or a positive drug screen

5. Poor venous access and unable to donate blood

6. Donated blood within 56 days of study dosing

7. Donated plasma within 7 days of study dosing

8. Taken an_ _rescri_tion medications or over-the-counter medications including herbal products within 28 days of commencing study dru_ dosin_ with the exce_tion of vitamins and/or acetaminophen and/or ibuprofen and/or hormonal contraceptive medications

9. History of significant drug sensitivity or drug allergy

10. Known hypersensitivity to the study drugs, the metabolites or formulation excipients

11. Treated with systemic steroids, immunosuppressant therapies or chemotherapeutic agents within 3 months of study screening, or expected to receive these agents during the study (eg, corticosteroids, immunoglobulins, and other immune- or cytokine-based therapies)

12. History of recurring syncope, palpitations, or recurring, unexplained dizziness

13. Implanted defibrillator or pacemaker

14. Inappropriate for study participation for any reason, in the opinion of the investigator

15. Participation in any other clinical trial (including observational trials) without prior approval from the sponsor was prohibited while participating in this trial

16. Any other clinical condition or prior therapy that, in the opinion of the investigator, would make the subject unsuitable for the study or unable to comply with dosing requirements

7.3.3. Removal of Subjects from Therapy or Assessment

Subjects could withdraw or be removed from treatment for any of the following reasons:

- Intercurrent illness that, in the judgment of the investigator, affected assessments of clinical status to a significant degree
- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromised the ability to continue study-specific procedures or was considered to not be in the subject's best interest
- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study (refer to Appendix 4 of the protocol, Appendix 16.1.1)
- Investigator discretion
- Discontinuation of the study at the request of Gilead, a regulatory agency, or an IRB

7.4. Study Treatments

7.4.1. Treatments Administered

There were 3 study treatments, as follows:

- **Treatment A:** Single dose of FTC/RPV/TAF (200/25/25 mg) FDC tablet administered orally under fed conditions
- **Treatment B:** Single dose of Edurant (RPV 25-mg tablet) administered orally under fed conditions
- **Treatment C:** Single dose of E/C/F/TAF (150/150/200/10 mg) FDC tablet administered orally under fed conditions

Each subject was scheduled to receive all 3 treatments according to the randomization scheme (Section 7.4.3). The study drugs were administered on Days 1, 15, and 29.

The treatment sequences are shown in Table 7-1.

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/s/

GAJENDIRAN MAHADEVAN
01/05/2016

ARINDAM DASGUPTA
01/05/2016

CHARLES R BONAPACE
01/05/2016

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:	September 23, 2015
Requesting Office or Division:	Division of Antiviral Products (DAVP)
Application Type and Number:	NDA 208351
Product Name and Strength:	Odefsey (emtricitabine, rilpivirine, and tenofovir alafenamide) Tablets 200 mg/25 mg/25 mg
Product Type:	Multi-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Gilead Sciences, Inc.
Submission Date:	July 1, 2015
OSE RCM #:	2015-1505
DMEPA Primary Reviewer:	Mónica Calderón, PharmD, BCPS
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD

1 REASON FOR REVIEW

Gilead Sciences, Inc. submitted a new drug application (NDA 208351) for the treatment of HIV-1 infection in (b) (4) patients 12 years of age and older with no antiretroviral treatment history or who have virologically suppressed to replace (b) (4) antiretroviral (b) (4) regimen. Thus, the Division of Antiviral Products (DAVP) requested DMEPA evaluate the Applicant's proposed full prescribing information (FPI), patient package insert (PPI) and container labels. The Applicant also submitted carton labeling and container labels for the Gilead Access Program with this submission.

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 (N/A)
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 label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant is proposing a multi-ingredient, single-strength tablet available as, 200 mg/25 mg/25 mg. The tablets will be packaged in 30-count bottles, which are supported by the dosage and administration of this product. DMEPA performed a risk assessment of the proposed commercial container label, the FPI, and PPI.

We determined that important information is displayed clearly on the proposed commercial container label, in the Dosage and Administration section within the FPI, and the "How Should I Take [TRADENAME]" section within the PPI. Our review of the carton labeling and container (b) (4) (b) (4) Our only recommendation is that all labels and labeling should be updated to reflect the conditionally acceptable proprietary name, Odefsey.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes the labels and labeling are acceptable from a medication error perspective. We only recommend that the "TRADENAME' statement be replaced with the conditionally acceptable proprietary name, Odefsey, where applicable throughout the labels and labeling. See section 4.1, below, for our recommendations.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. General Recommendation

Replace "TRADENAME" with the conditionally acceptable proprietary name, Odefsey, where applicable throughout the labels and labeling.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Odefsey that Gilead Science, Inc. submitted on September 4, 2015.

Table 2. Relevant Product Information for Odefsey	
Active Ingredient	Emtricitabine, rilpivirine, and tenofovir alafenamide
Indication	Treatment of HIV-1 infection in (b) (4) patients 12 years of age and older with no antiretroviral treatment history or who have virologically suppressed to replace (b) (4) (b) (4) antiretroviral (b) (4) regimen.
Route of Administration	Oral
Dosage Form	Tablet
Strength	200 mg/25 mg/25 mg
Dose and Frequency	One tablet once daily
How Supplied	Each bottle contains 30 tablets.
Storage	Store below 30 °C (86 °F)

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,[1] along with postmarket medication error data, we reviewed the following Odefsey labels and labeling submitted by Gilead Sciences, Inc on July 1, 2015.

- Container label
- Carton labeling

G.2 Label and Labeling Images

Commercial Label

(b) (4)

[redacted]

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

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

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/s/

MONICA M CALDERON
09/23/2015

BRENDA V BORDERS-HEMPHILL
09/24/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 208351 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: emtricitabine, rilpivirine, tenofovir alafenamide Established/Proper Name: Dosage Form: FDC tablet Strengths: 200/25/25		
Applicant: Gilead Sciences, Inc. Agent for Applicant (if applicable): n/a		
Date of Application: July 1, 2015 Date of Receipt: July 1, 2015 Date clock started after UN:		
PDUFA/BsUFA Goal Date: March 1, 2016	Action Goal Date (if different):	
Filing Date: August 30, 2015	Date of Filing Meeting: July 27, 2015	
Chemical Classification (original NDAs only) : ☒ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication: For the treatment of HIV-1 infection in (b) (4) 12 years of age or older.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☐ Standard ☒ Priority ☐ Pediatric WR ☐ QIDP ☒ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 53971, IND 63737, IND 67671, IND 103093, IND 111077, IND 106252 for Complera, Janssen's IND 67699 for rilpivirine and IND 75391 for Simeprevir.	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also,***	☒	☐		

ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** *http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm* ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** *http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm*	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov)*: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf*	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**

Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted questions below:	☐	☒		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested:3 or 5 years	☒	☐	☐	TAF is NME currently under review under 3 different NDAs. If this is approved first,

Note: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*				sponsor has requested 5 years of exclusivity
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☐	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

(*BLAs/BLA efficacy supplements*) including: ☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the***	☒	☐		

supporting document category, "Form 3674." ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2]	☒	☐		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm

***Note**: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)[3]***	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837 htm

Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?[5]	☒	☐	☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)?	☐	☐	☐	

[4] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

[5] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If no, request in 74-day letter.				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☒	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		preliminary comments sent; sponsor canceled meeting
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 27, 2015

BACKGROUND: The new molecular entity, tenofovir alafenamide is currently under review in three new drug applications (NDA 207561, 208215, and 208351). New drug application 208351 for emtricitabine, rilpivirine, and tenofovir alafenamide FDC tablet for the treatment of HIV-1 infection in (b) (4) 12 years and older was received on July 1, 2015 from Gilead Sciences. The pivotal data to support the use of this product is from a bioequivalence study. The sponsor submitted the application with a tropical disease voucher giving it a priority review. Tenofovir alafenamide has not yet been approved so it is considered an NME and will be reviewed under PDUFA V's "The Program".

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Christian Yoder	Y
	CPMS/TL:	Karen Winestock	Y
Cross-Discipline Team Leader (CDTL)	Islam Younis		N
Division Director/Deputy	Debra Birnkrant		Y
Office Director/Deputy	Edward Cox		N
Clinical	Reviewer:	Bill Tauber	Y
	TL:	Russell Fleischer	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	Lisa Naeger	Y
	TL:	Julian O'Rear	Y
Clinical Pharmacology	Reviewer:	Mario Sampson	Y
	TL:	Islam Younis	N

• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:		
	TL:		

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Mark Seaton	Y
	TL:	Hanan Ghantous	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Stephen Miller	Y
	RBPM:	Florence Aisida	N
• Drug Substance	Reviewer:	Haripada Sarker	Y
• Drug Product	Reviewer:	Stephen Miller	Y
• Process	Reviewer:	Stephen Frisbee	Y
• Microbiology	Reviewer:		
• Facility	Reviewer:	Rose Xu	Y
• Biopharmaceutics	Reviewer:	Om Anand	Y
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)	EA Reviewer: James Laurenson		N
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Morgan Walker	N
	TL:	Barbara Fuller	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Jessica Fox	N
	TL:	Eunice Chung-Davies	N
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Monica Calderon	Y
	TL:	Vicky Borders-Hemphill	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:		
	TL:		
Other attendees – OND ADRA	Stacy Min, PharmD, Associated Director for Labeling		Y
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: This drug is not first in its class
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity</u> (NDAs only) • Is the product an NME?	 ☒ YES ☐ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? **Comments**: 2 facilities scheduled to be inspected in (b) (4)	☐ Not Applicable ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☐ YES ☒ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	none
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Division; Division Deputy Director Jeffrey Murray (TAF expected to be approved before signoff and will no longer be an NME) **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): September 29, 2015 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**: Meetings: Mid cycle – 9/29/15, Wrap-Up – 1/25/16	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. Review Classification: ☐ Standard Review ☒ Priority Review
ACTION ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTIAN P YODER
08/10/2015

KAREN D WINESTOCK
08/12/2015