

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208215Orig1s000

OTHER REVIEW(S)

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: March 25, 2016
Requesting Office or Division: Division of Antiviral Products (DAVP)
Application Type and Number: NDA 208215
Product Name and Strength: Descovy
(emtricitabine and tenofovir alafenamide) Tablets
(b) (4) 200 mg/25 mg
Submission Date: January 11, 2016 and March 22, 2016
Applicant/Sponsor Name: Gilead Sciences, Inc.
OSE RCM #: 2015-819-1
DMEPA Primary Reviewer: Mónica Calderón, PharmD, BCPS
DMEPA Team Leader: Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

Gilead has submitted the revised container label and carton labeling (Appendix A) for Descovy 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.

Container Labels

Gilead submitted a revised container label and carton labeling for the 200 mg/25 mg strength tablets. The boxed strength statement is now a different color from the colors used to highlight the added strengths of the Truvada product line.

¹ Calderon M. Label and Labeling Review for Descovy (NDA 208215). 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 Dec 08. 32 p. OSE RCM No.: 2015-819.

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/s/

MONICA M CALDERON
03/25/2016

BRENDA V BORDERS-HEMPHILL
03/25/2016

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 # 208215/Original 1
Product Name: DESCOVY[®] (emtricitabine and tenofovir alafenamide) 200/25 mg fixed-dose combination (FDC) tablet

PMR Description: Conduct your deferred pediatric study in HIV-1 infected patients 4 weeks to less than 6 years of age to assess the pharmacokinetics, safety and tolerability, and antiviral activity of an age-appropriate formulation of emtricitabine and tenofovir alafenamide given in combination as DESCOVY fixed dose combination product. Study participants should be monitored for 24 to 48 weeks to assess safety and durability of antiviral response.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>12/31/2017</u>
	Study/Trial Completion:	<u>12/31/2019</u>
	Final Report Submission:	<u>4/30/2020</u>
	Other: _____	<u>MM/DD/YYYY</u>

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 study is to determine the PK profile of emtricitabine (F) and tenofovir alafenamide (TAF) combined together in the fixed dose combination DESCovy (F/TAF) in pediatric patients 4 weeks to less than 6 years of age, confirm the dose that results in exposure similar to that found to be safe and effective in adult and older pediatric patients, and provide safety information in this pediatric age group. An assessment of antiviral activity will be performed to further support extrapolation of efficacy from the adult clinical trials. In adults, the dosage of TAF (b) (4) when DESCovy is given in combination with a CYP3A inhibitor such as cobicistat or ritonavir or 25mg when DESCovy is combined with other ARV not containing a CYP3A inhibitor. One of the goals of the deferred study is to confirm the TAF exposures resulting from combination with other ARVs in this patient population.

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.

This single arm, open label, study will be conducted in HIV-infected patients 4 weeks to less than 6 years of age to assess the pharmacokinetics, safety and tolerability, and antiviral activity of age-appropriate doses of the fixed dose combination DESCOPY (emtricitabine and tenofovir alafenamide). Subjects > 2 years of age must be fully suppressed and stable on their preceding regimen with no known viral resistance and will switch from their prior 2 NRTI combination to DESCOPY while continuing the third antiretroviral drug. Those < 2 years may switch from a suppressive treatment regimen or initiate treatment with DESCOPY plus another antiretroviral drug. The doses to be evaluated will be established following the availability of PK data from the study in patients 6 years to less than 18 years of age and will be confirmed in preliminary lead-in pharmacokinetic phases in cohorts of subjects 2 to < 6 years and then 4 weeks to < 2 years of age.

Required

- Observational pharmaco-epidemiologic 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)
- 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.

(signature line for BLAs)

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 # 208215/Original 1
Product Name: DESCOVY[®] (emtricitabine and tenofovir alafenamide) 200/25 mg fixed-dose combination (FDC) tablet

PMR Description: Conduct your deferred pediatric study in HIV-1 infected, virologically suppressed patients 6 years to less than 12 years of age switching from other nucleoside reverse transcriptase inhibitors (NRTIs) to assess the pharmacokinetics, safety, tolerability and antiviral activity of age-appropriate DESCOVY tablets in combination with an approved third antiretroviral drug. Study participants should be monitored for 48 to 96 weeks to assess safety and durability of antiviral response.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>Submitted</u>
	Study/Trial Completion:	<u>12/31/2017</u>
	Final Report Submission:	<u>06/30/2018</u>
	Other:	<u>MM/DD/YYYY</u>

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 study is to determine the PK profile of emtricitabine (FTC) and tenofovir alafenamide (TAF) combined together in the fixed drug combination DESCovy (F/TAF) in pediatric patients 6 to less than 12 years of age, confirm the dose that results in exposure similar to that found to be safe and effective in adult patients, and provide safety information in this pediatric age group. An assessment of antiviral activity will be performed to further support extrapolation of efficacy from the adult clinical trials. In adults, the dosage of TAF (b) (4) when DESCovy is given in combination with a CYP3A inhibitor such as cobicistat or ritonavir or 25mg when DESCovy is combined with other ARV not containing a CYP3A inhibitor. One of the goals of the deferred study is to confirm the TAF exposures generated in combination with other ARVs in the pediatric population conform to what was observed in adult patients.

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
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- 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.

This open label, multicenter, comparative, switch study will be conducted in HIV-infected patients 6 years to less than 18 years to assess the pharmacokinetics, safety and tolerability and antiviral activity of age-appropriate doses of the fixed dose combination DESCovy (emtricitabine and tenofovir alafenamide, F/TAF). Subjects must be fully suppressed and stable on their preceding regimen with no known viral resistance. In Cohort 1, 12 to < 18 year old subjects will be switched from other 2-drug NRTI regimens (N=25) to F/TAF. This age group will be labeled in the current NDA but is also included in this protocol. In Cohort 2, 6 to < 12 year old subjects will be randomized 2:1 to switch to F/TAF or F/TDF from other 2-drug NRTI regimens (N=75). In both cohorts, subjects will remain on their original third antiretroviral drug. Although the study includes patients in two pediatric age cohorts, only Cohort 2 is the subject of the PMR.

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)
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Continuation of Question 4

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

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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)

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/s/

MYUNG JOO P HONG
03/25/2016

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

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

Memorandum

Date: March 15, 2016

To: Myung-Joo Patricia Hong, MS, Senior Regulatory Project Manager
Division of Antiviral Products

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

Subject: NDA 208215 – DESCOPY (emtricitabine and tenofovir
alafenamide) tablets, for oral use

As requested in the Division of Antiviral Products' (DAVP) consult dated April 9, 2015, the Office of Prescription Drug Promotion (OPDP) has reviewed the DESCOPY prescribing information, patient labeling, and carton/container labeling.

OPDP reviewed the proposed substantially complete version of the prescribing information sent via email on March 7, 2016, and has provided comments in the labeling attached to this document.

The Division of Medical Policy Programs and OPDP provided a single, consolidated review of the patient labeling on March 15, 2016.

OPDP reviewed the carton/container labeling received in the EDR on January 11, 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
03/15/2016

**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: March 15, 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)
Sharon R. Mills, BSN, RN, CCRP
Acting Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Morgan Walker, PharmD, MBA
Senior 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): DESCOVY (emtricitabine and tenofovir alafenamide)

Dosage Form and Route: tablets

Application Type/Number: NDA 208215

Applicant: Gilead Sciences, Inc.

1 INTRODUCTION

On April 7, 2015, Gilead Sciences, Inc. submitted for the Agency's review an original New Drug Application (NDA) 208215 for DESCOVY (emtricitabine and tenofovir alafenaide) tablets. The proposed indication for DESCOVY (emtricitabine and tenofovir alafenaide) tablets is for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antiviral Products (DAVP) on April 9, 2015 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for DESCOVY (emtricitabine and tenofovir alafenaide) tablets.

2 MATERIAL REVIEWED

- Draft DESCOVY (emtricitabine and tenofovir alafenaide) tablets PPI received on April 7, 2015, revised by the Review Division throughout the review cycle, further revised by the Applicant, and received by DMPP and OPDP on March 4, 2016.
- Draft DESCOVY (emtricitabine and tenofovir alafenaide) tablets Prescribing Information (PI) received on April 7, 2015, revised by the Review Division throughout the review cycle, further revised by the Applicant, and received by DMPP and OPDP on March 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 APFont 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
03/15/2016

JESSICA M FOX
03/15/2016

SHARON R MILLS
03/15/2016

LASHAWN M GRIFFITHS
03/15/2016

MEMORANDUM

**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 NDA 208215 Emtricitabine/
Tenofovir Alafenamide (200/25 mg) FDC Tablets and 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 GS-US-311-1473 (NDA 208215) and GS-US-366-1159 (NDA 208351) at [REDACTED] (b) (4)

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

revealed that an adverse event and subsequent concomitant medications for subject 1024 (study GS-US-311-1473) were not reported to the sponsor and study monitor and 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 studies GS-US-311-1473 and GS-US-366-1159 be accepted for further Agency review. The final classification for this inspection is no action indicated (NAI).

Application

Type & Number: NDA 208215
Study #: GS-US-311-1473
Study Title: "A phase 1, randomized, open-label, single-dose, two-way cross-over study to evaluate the bioequivalence of Emtricitabine and Tenofovir Alafenamide between Emtricitabine and Tenofovir Alafenamide (200/25 mg) and Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (150/150/200/10 mg) fixed-dose combination tablets"

Dates of Study Conduct: June 30-August 25, 2014

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 [REDACTED] (b) (4)

[REDACTED] 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 an adverse event and subsequent concomitant medications for subject 1024 (study GS-US-311-1473) were not reported to the sponsor and study monitor and subject 1088 (study GS-US-366-1159) may have been taking prescription medication on the day of admission to the clinical site.

Subject 1024 (Study GS-US-311-1473) - This subject experienced rectal bleeding just prior to discharge from the clinical site on July 23, 2014. The principal investigator documented this adverse event as not related to the study drug and advised the subject to purchase over-the-counter medicines (Dulcolax and Preparation H) to treat the rectal bleeding. Information of the over-the-counter medications was reported on the Outpatient Concomitant Medication Treatment Record, but the sponsor and study monitor was not informed of the adverse event or the concomitant medications (**Attachment-1**).

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 adverse event/concomitant medications for subject 1024 and prescription medication for subject 1088.
- Following the evaluation of the inspectional findings and the EIR, the clinical data from studies GS-US-311-1473 and GS-US-366-1159 were found to be reliable. Therefore, I recommend that the data generated at [REDACTED] (b)(4) [REDACTED] be accepted for further Agency review.

Gajendiran Mahadevan, Ph.D.
DNDBE, OSIS

Final Classification:

NAI: [REDACTED] (b)(4)
FEI#: [REDACTED] (b)(4)

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

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

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ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/Seaview Jacksonville, Jacksonville, FL/NDA 208215_
Emtricitabine

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CHARLES R BONAPACE
01/05/2016



NDA 208215

LABELING PMR/PMC DISCUSSION COMMENTS

Gilead Sciences, Inc.
Attention: Patricia Carlos
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Carlos:

Please refer to your New Drug Application (NDA) dated April 6, 2015, received April 7, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for DESCOVY (emtricitabine and tenofovir alafenamide) (b) (4) 200/25 mg fixed-dose combination tablets.

On November 6, 2015, we received your proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by January 11, 2016. The resubmitted labeling will be used for further labeling discussions.

Your proposed prescribing information (PI) must conform to the content and format regulations found at [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

We have the following comments from the review team. These comments refer to our recommended labeling changes for carton and container labeling.

Container Label and Access Container Label and Carton Labeling

1. As presented, the labels and labeling for both strengths use the same colored gray box around the strength statement. Please revise the colored box for one of the strengths to a dissimilar color other than gray to help differentiate the labels and labeling to prevent strength selection errors. Additionally, ensure the colors used for your Descovy product line are distinguishable from the colors used in your Truvada product line.
2. Replace “TRADENAME” with the conditionally acceptable proprietary name, Descovy.
3. Revise the active ingredients to read as follows, “emtricitabine and tenofovir alafenamide.”

If you have any questions, call me at (301) 796-0807.

Sincerely,

{See appended electronic signature page}

Myung-Joo Patricia Hong, M.S.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE: Labeling

28 Pages of Draft Labeling have been
Withheld in Full as b4 (CCI/TS)
immediately following this page

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

/s/

MYUNG JOO P HONG
12/17/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review: December 8, 2015

Requesting Office or Division: Division of Antiviral Products (DAVP)

Application Type and Number: NDA 208215

Product Name and Strength: Descovy
(emtricitabine and tenofovir alafenamide) Tablets
[REDACTED] (b) (4) 200 mg/25 mg

Product Type: Multi-Ingredient Product

Rx or OTC: Rx

Applicant/Sponsor Name: Gilead Sciences, Inc.

Submission Date: April 7, 2015

OSE RCM #: 2015-819

DMEPA Primary Reviewer: Mónica Calderón, PharmD, BCPS

DMEPA Team Leader: Vicky Borders-Hemphill, PharmD

DMEPA Associate Director: Irene Z. Chan, PharmD, BCPS

1 REASON FOR REVIEW

Gilead Sciences, Inc. submitted a new drug application (NDA 208251) for the treatment of HIV-1 infection in adults in combination with other antiretroviral agents. Thus, the Division of Antiviral Products (DAVP) requested DMEPA evaluate the Applicant's proposed full prescribing information (FPI) 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
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

Gilead Sciences, Inc. is proposing (b) (4) 200 mg/25 mg), fixed dose, multiple ingredient tablets of emtricitabine and tenofovir alafenamide. The daily dose is one 200 mg/25 mg tablet; (b) (4)

The product will be packaged in 30-count bottles, which is supported by the dosage and administration of this product.

DMEPA performed a risk assessment of the proposed container labels, Patient Package Insert (PPI), and FPI and determined the Dosage and Administration section is clear; however, the strengths are not clearly differentiated on the container labels and carton labeling. We provide recommendations in Section 4.2 to mitigate the risk for strength selection errors and to update the FPI to reflect the conditionally acceptable proprietary name, Descovy.

The submission also contained container labels and carton labeling for Gilead Access Program products. Our review of the carton labeling and container labels determined that the labels and labeling are identical to the commercial products with the exception of the added statement “Gilead Access Program”; thus, the same recommendations for the commercial packaging will apply.

Naming of Antiviral Products with Multiple Active Ingredients

We considered whether the order of listing for the active ingredients, and hence, the order of strengths of the individual ingredients, may contribute to medication errors.

Gilead currently lists the active ingredients in alphabetical order in the FPI as well as on the container label. DAVP’s general recommendation for naming of antiviral products with multiple active ingredients is to list by alphabetical order. One exception is when one active ingredient is a pharmacokinetic (PK) booster (e.g., ritonavir, cobicistat) boosted by including a cytochrome P450 inhibitor; in this case the PK booster cytochrome inhibitor will be listed directly after the drug that is being boosted. Active ingredient names typically are separated by commas plus “and” (e.g., “active1 and active2” or “active1, active2, and active3”). Strengths are typically separated with slashes on container labels.

For this product, the first strength is the higher fixed dosage strength and the lower variable strength is listed as the second strength. We considered whether this naming convention poses risk for strength selection errors, especially in computer provider order entry (CPOE) systems. The first strength is likely to be the primary expression of the product strength when written and the second strength may be dropped. Per the Institute of Safe Medication Practices (ISMP) Med-E.R.R.S. August 2004 survey, “Prescribing Combination Products”, practitioners indicated that both strengths for combination products are not always written regardless of whether both ingredients vary (24%) or if one ingredient has a fixed dosage strength and the other ingredient has a varying dosage strength (49%).¹ (b) (4)

This minimizes the risk for wrong strength error.

We considered whether having the fixed dosage strength (200 mg) presented first reduces the likelihood of selecting the proper strength of Descovy in CPOE systems since the first strength is likely to be seen first during computer order entry for procurement, prescribing, and dispensing. For fixed dose combination products with a fixed dosage strength, if both strengths are listed next to each other in a drop down selection menu, the health care practitioner will have to first look past three same numerical digits, 200 mg, to see the difference in the variable strengths listed next.

¹ ISMP August 2004 Question- ERR survey on Prescribing Combination Products: <http://www.mederrs.com/Question/Resulterr0408.asp>

If the varying dosage strength were listed first, the ordering provider may more readily distinguish the appropriate strength to select. However, while we do have these concerns, our research identified there are several currently marketed fixed dose combination products where the first strength is the fixed dosage strength and the second strength is the variable strength (e.g., Liptruzet, Vytorin, Caduet, etc). To date, we have not seen any medication error reports related to the fixed dosage strength being listed first within a fixed dose combination tablet with multiple strengths. Therefore, at this time, we do not recommend any changes and will monitor for any postmarketing errors.

Confusion between Truvada and Descovy

We considered the risk for confusion between Truvada (emtricitabine and tenofovir disoproxil fumarate) and Descovy (emtricitabine and tenofovir alafenamide) due to both products containing tenofovir prodrugs. We also considered the risk for confusion if a provider does not use the proprietary name when prescribing but instead uses a shortened version of the established names, such as tenofovir with emtricitabine, or the antiretroviral drug abbreviations, TDF FTC.

Descovy contains a different prodrug of tenofovir, tenofovir alafenamide, than the prodrug in the currently marketed Truvada, tenofovir disoproxil; however, both products are similar in terms of efficacy and safety. As noted by the clinical reviewer in an email dated October 6 and discussed in a telephone conversation with the clinical team leader on October 6, 2015, if an accidental substitution were to occur with Truvada for Descovy, there would likely be no perceptible effect associated. Also, if a patient was prescribed Descovy and accidentally received a single dose of Truvada, it is unlikely an adverse event or emergent viral resistance outcome would occur. The concern of a measureable effect occurs with prolonged substitution of a month or longer which may lead to noticeable renal and/or bone mineralization adverse impact. Of note, drug interactions involving tenofovir alafenamide and select protease inhibitors requiring Descovy to be dose adjusted may also be of concern if Descovy were to be dispensed in place of Truvada.

The tenofovir prodrug contained in Truvada is a different strength than the tenofovir prodrug contained in Descovy with no numerical overlap or similarity in strengths. (b) (4)

[REDACTED] Truvada, which is currently only available in a single strength of 200 mg/300 mg. This will help to mitigate the risk for wrong drug selection errors between Descovy and Truvada. In addition to the above, we recommend a statement be added in the FPI to indicate the two prodrugs should not be substituted for each other to further mitigate selection errors. We provide recommendations in Section 4.1.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes Gilead's proposed PPI and FPI are acceptable. However, to minimize the potential for strength selection errors, we provide recommendations to add language in the FPI

to indicate the two prodrugs should not be substituted for one another in Section 4.1 and we provide recommendations to differentiate the container labels for the two strengths in Section 4.2. The same recommendations should be applied to the Gilead Access labels and labeling. We also recommend updating the FPI and labels and labeling with the conditionally acceptable proprietary name, Descovy, in Sections 4.1 and 4.2, respectively. We advise the recommendations below are implemented prior to approval of this application.

4.1 RECOMMENDATIONS TO THE DIVISION

Full Prescribing Information

1. We provide recommended revisions to the Division's working FPI document (see Appendix G) to revise the D&A section and Highlights section.
2. Replace "TRADENAME" with the conditionally acceptable proprietary name, Descovy.

4.2 RECOMMENDATIONS FOR GILEAD SCIENCES, INC.

We recommend the following be implemented prior to approval of this NDA:

Commercial Container Label and Access Container Label and Carton Labeling

1. As presented, the labels and labeling for both strengths use the same colored gray box around the strength statement. Revise the colored box for one of the strengths to a dissimilar color other than gray to help differentiate the labels and labeling to prevent strength selection errors. Additionally, ensure the colors used for your Descovy product line are distinguishable from the colors used in your Truvada product line.
2. Replace "TRADENAME" with the conditionally acceptable proprietary name, Descovy.
3. Revise the active ingredients to read as follows, "emtricitabine and tenofovir alafenamide".

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Descovy that Gilead Science, Inc. submitted on July 8, 2015.

Table 2. Relevant Product Information for Descovy	
Active Ingredient	Emtricitabine and tenofovir alafenamide
Indication	Treatment of HIV-1 infection in adults in combination with other antiretroviral agents.
Route of Administration	Oral
Dosage Form	Tablet
Strength	(b) (4) 200 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,² along with postmarket medication error data, we reviewed the following Descovy labels and labeling submitted by Gilead Sciences, Inc on July 8, 2015.

- FPI
- Container label
- Carton labeling

G.2 Label and Labeling Images

FPI- Highlights and Dosage and Administration Section

-----**DOSAGE AND ADMINISTRATION**-----

(b) (4)



² Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

MONICA M CALDERON
12/08/2015

BRENDA V BORDERS-HEMPHILL
12/08/2015

IRENE Z CHAN
12/10/2015

M E M O R A N D U M

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

DATE: September 8, 2015

TO: Director, Investigations Branch
Florida District Office
555 Winderley Place
Suite 200
Maitland, FL 32751

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

SUBJECT: **FY 2015, CDER High Priority User Fee NDA, Pre-Approval
Data Validation Inspection**, Bioresearch Monitoring,
Human Drugs, CP 7348.001

This inspection memo provides pertinent information to conduct the inspection of the following bioavailability studies. Background material is available in ECMS under the ORA FLA-DO folder. The inspection should be completed and endorsed EIR submitted to CDER prior to **November 29, 2015**.

Do not reveal the studies to be inspected, drug name, or the study investigator to the site prior to the start of the inspection. The site will receive this information during the inspection opening meeting. The inspection will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, not under CP 7348.811 (Clinical Investigators).

At the completion of the inspection, please send a scanned copy of the completed sections A and B of this memo to the OSIS POC.

Clinical Site:



Application #: NDA 208215

Drug: Emtricitabine/Tenofovir Alafenamide (200/25 mg)

Study Number: GS-US-311-1473

Study Title: "A Phase 1, Randomized, Open-Label, Single-Dose, Two-Way Cross-Over Study to Evaluate the Bioequivalence of Emtricitabine and Tenofovir Alafenamide between Emtricitabine/Tenofovir Alafenamide (200/25 mg) and Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (150/150/200/10 mg) Fixed-Dose Combination Tablets."

Investigator: Stuart I. Harris, MD, PhD

TEL: 904-730-4740 Ext. 5077

Email: (b) (4)

of subjects: 116

Application #: NDA 208351

Drug: Emtricitabine/Rilpivirine/Tenofovir Alafenamide (200/25/25 mg)

Study Number: 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)."

Investigator: Chrysoula Pappa, MD

TEL: 904-730-4740 Ext. 5078

Email: (b) (4)

of subjects: 96

Please collect a list of bioequivalence studies performed at the site in the last 5 years. The list should include information on test and reference reserve samples retained at the site or at a third party for the bioequivalence studies. Please refer to **Table 1** for an example.

SECTION A - RESERVE SAMPLES

Reserve samples:

Because studies GS-US-311-1473 and GS-US-366-1159 are bioavailability studies and not bioequivalence studies, there is no regulatory requirement for storage of reserve samples. However, CDER review division has requested collection of reserve samples for studies GS-US-311-1473 and GS-US-366-1159.

During the clinical site inspection, please:

- Verify that the site retained reserve samples. **Because there is no regulatory requirement, Form FDA 483 should not be issued to the site if the site did not retain reserve samples for studies GS-US-311-1473 and GS-US-366-1159.**
- If the reserve samples were stored at a third party site, collect an affidavit to confirm that the third party is independent from the applicant, manufacturer, and packager. Additionally, verify that the site notified the applicant, in writing, of the storage location of the reserve samples.
- Obtain written assurance from the clinical investigator or the responsible person at the clinical site that the reserve samples are representative of those used in the specific studies, and that samples were stored under conditions specified in accompanying records.
- Collect and ship samples of the test and reference drug products **in their original containers** to the following address:

John Kauffman, Ph.D.
Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
645 S. Newstead Ave
St. Louis, MO 63110
TEL: 1-314-539-2135

SECTION B - CLINICAL DATA AUDIT

Please remember to collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

- Confirm that informed consent was obtained for 100% of subjects enrolled.
- Randomly select and audit the study records for at least 40 subjects enrolled in **Study GS-US-311-1473** and at least 40 subjects enrolled in **Study GS-US-366-1159**.
- Compare the study reports submitted to FDA with the original documents at the site.
- Check for under-reporting of adverse events (AEs).
- Check for evidence of inaccuracy in the electronic data capture system.
- Check reports for the subjects audited.
 - o Number of subject records reviewed during the inspection: _____
 - o Number of subjects screened at the site: _____
 - o Number of subjects enrolled at the site: _____
 - o Number of subjects completing the study: _____
- Confirm that site personnel conducted clinical assessments in a consistent manner and in accordance with the study protocols.
- Confirm that site personnel followed SOPs during study conduct.
- Examine correspondence files for any applicant or monitor-requested changes to study data or reports.
- Confirm that adequate corrective actions were implemented for observations cited during the last inspection (if applicable).
- Include a brief statement summarizing your findings including IRB approvals, study protocol and SOPs, protocol deviations, AEs, concomitant medications, adequacy of records, inclusion/exclusion criteria, drug accountability documents, and case report forms for dosing of subjects, etc.
- Other comments:

Additional instructions to the ORA Investigator:

In addition to the compliance program elements, other study specific instructions may be provided by the OSIS POC prior to

commencement of the inspection. Therefore, we request that the OSIS POC be contacted for any further instructions, inspection related questions or clarifications before the inspection and also regarding any data anomalies or questions noted during review of study records on site.

If you issue Form FDA 483, please forward a copy to the OSIS POC (see below). If it appears that the observations may warrant an OAI classification, notify the OSIS POC as soon as possible.

Remind the inspected site of the 15 business-day timeframe for submission of a written response to the Form FDA 483. In addition, please forward a copy of the written response as soon as it is received to the OSIS POC.

OSIS POC: Yiyue Zhang, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance
Tel: 1-240-402-6559
Fax: 1-301-847-8748
E-mail: yiyue.zhang@fda.hhs.gov

The endorsed EIR should be sent to the following address:

Ms. Venese Dejernett
FDA/CDER/OTS/OSIS
W051 RM5318 HFD-45
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
1-301-796-0650
venese.dejernett@fda.hhs.gov

Email cc:
ORA/SE-FO/FLA-DO/Sinninger
OSIS/Taylor/Dejernett/Fenty-Stewart/Nkah/Johnson
OSIS/DNDBE/Bonapace/Dasgupta/Cho/Zhang
OSIS/DGDBE/Haidar/Skelly/Choi

Draft: YZ 9/1/2015
Edit: AD 9/8/2015, CB 9/8/2015
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical
Sites/ (b) (4)

BE file#: 6894, 6943
FACTS: 11537416

Table 1

SL NO.	Study number	Drug Name	Fast/Fed	Sponsor	Submission	Study Conduct Dates	Reserve Samples	Quantity	Lot# for Test and Reference
1	XXXXX	(b) (4)	Fast	XXXX	USFDA	(b) (4)	(b) (4)	(b) (4)	XXXX and XXX
2	XXXXX	Montelukast	Fed	XXXXX	unknown	XXXXX			XXXX and XXX
3	XXXXX	XXXXXXXX	Fast	XXXXXX	Pilot	XXXXX			XXXX and XXX

Yiyue Zhang -S

Digitally signed by Yiyue Zhang -S
 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
 cn=Yiyue Zhang -S, 0.9.2342.19200300.100.1.1=2001741289
 Date: 2015.09.08 11:07:45 -04'00'

Yiyue Zhang, Ph.D.
 Division of New Drug Bioequivalence Evaluation
 Office of Study Integrity and Surveillance

Arindam Dasgupta -S

Digitally signed by Arindam Dasgupta -S
 DN: c=US, o=U.S. Government, ou=HHS,
 ou=FDA, ou=People,
 0.9.2342.19200300.100.1.1=0012329705,
 cn=Arindam Dasgupta -S
 Date: 2015.09.08 11:27:23 -04'00'

Arindam Dasgupta, Ph.D.
 Division of New Drug Bioequivalence Evaluation
 Office of Study Integrity and Surveillance

Charles R. Bonapace -S

Digitally signed by Charles R. Bonapace -S
 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
 ou=People, 0.9.2342.19200300.100.1.1=1300156609,
 cn=Charles R. Bonapace -S
 Date: 2015.09.08 11:31:51 -04'00'

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

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/s/

YIYUE ZHANG
09/10/2015

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 #: 208215	NDA Supplement #: N/A	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Animal Rule Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Pediatric
Proprietary Name: DESCOVY Established/Proper Name: emtricitabine/tenofovir alafenamide (F/TAF) Dosage Form: Fixed-dose combination tablets Strengths: (b) (4) 200/25 mg		
Applicant: Gilead Sciences, Inc. Agent for Applicant (if applicable):		
Date of Application: April 6, 2015 Date of Receipt: April 7, 2015 Date clock started after UN:		
PDUFA Goal Date: April 7, 2016		Action Goal Date (if different):
Filing Date: June 6, 2015		Date of Filing Meeting: May 19, 2015
Chemical Classification (original NDAs only) : <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Treatment of HIV-1 infection in adults and pediatric patients 12years of age and older.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<i>The application will be a priority review if:</i>	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<i>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)</i>	
<i>The product is a Qualified Infectious Disease Product (QIDP)</i>	
<i>A Tropical Disease Priority Review Voucher was submitted</i>	
<i>A Pediatric Rare Disease Priority Review Voucher was submitted</i>	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	
<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division <i>(if OTC product)</i> :	
List referenced IND Number(s): IND 51285 and NDA 21356 for Viread (tenofovir disoproxil fumarate (TDF)) IND 53971 and NDA 21500 (capsule) and NDA 21896 (oral solution) for Emtriva (emtricitabine (F)) IND 63737 and NDA 207561 for TAF (tenofovir alafenamide) IND 67671 and NDA 21752 for Truvada (F/TDF) IND 103093 and f NDA 203100 for Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (E/C/F/TAF)) IND 101283 an NDA 203094 for Tybost (cobicistat) IND 111077 and NDA 207561 for E/C/F/TAF IND 118605 and NDA 204671 for Sovaldi (sofosbuvir) IND 111851 for F/TAF NDA 202123 for Complera (F/rilpivirine/TDF)	

NDA 203093 for Vitakta (elvitegravir)
 NDA 205834 for Harvoni (Ledipasvir/Sofosbuvir)

(b) (4)

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system? <i>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.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><i>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.</i></p>	<p>Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>):</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>
<p><i>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.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>
<p><u>User Fee Bundling Policy</u></p> <p><i>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</i></p>	<p>Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i></p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form, cover letter, and annotated labeling</i>). If yes, answer the bulleted questions below:	<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? 	<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> 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)]. 	<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> 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)]? <p><i>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.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <p><i>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</i></p> <p>If yes, please list below:</p>	<input type="checkbox"/>	<input type="checkbox"/>		

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	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Viread (tenofovir) was approved for orphan designation on March 17, 2009 for treatment of pediatric HIV infection.
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)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? If yes, # years requested: 5 yrs under “Umbrella Exclusivity” policy - if NDA 207561 is approved before NDA 208215 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
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)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>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</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> 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).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index : Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
BLAs only : Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Forms and Certifications				
<i>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.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>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].</i> <i>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..."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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? <i>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)</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>				
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u>				
Does the application trigger PREA?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i>				
<i>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.</i>				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				“Amended Agreed iPSP” submitted under IND 111851 on 4/30/15 - Agreement letter issued 5/28/15: Gilead will submit “Amended Agreed iPSP” to the appropriate section of NDA 208215
<u>BPCA:</u>				
Is this submission a complete response to a pediatric Written Request?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

Version: 3/20/2014

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Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Proprietary name grant letter issued 5/19/15
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format? ⁵	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
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?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult sent 4/9/15
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult sent 4/9/15
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult sent 4/9/15
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? If no, request in 74-day letter.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	OSI/BE consult sent 5/1/15
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): October 17, 2013 <i>If yes, distribute minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		EOP 2 Meeting scheduled under IND 111851; however, Gilead cancelled after receiving FDA's preliminary comments (10/15/13)
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): December 15, 2014 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
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ATTACHMENT

MEMO OF FILING MEETING

DATE: May 29, 2015

BACKGROUND:

DESCOVY is a two-drug fixed-dose combination (FDC) tablet consisting of emtricitabine and tenofovir alafenamide (F/TAF), both HIV nucleoside analog reverse transcriptase inhibitors (NRTIs), 200/ 25 mg (b) (4) tablets. Emtricitabine is approved as single-agent NDA and as part of fixed-dose combination tablet. Gilead Sciences (b) (4)

The proposed indication for DESCOVY is for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older. DESCOVY has a prescribing information (PI) and patient package information (PPI).

GENVOYA (NDA 207561) is also under review by the Division in a new FDC (elvitegravir/cobicistat/ emtricitabine / tenofovir alafenamide) with a PDUFA goal date of November 5, 2015. If GENVOYA is approved, then DESCOVY will not be considered an NME at the time of it's action.

- The trade name “DESCOVY®” was granted on May 19, 2015.
- Gilead requested a partial waiver of pediatric studies for children less than 4 weeks of age and a deferral of pediatric studies in children 4 weeks to less than 18 years of age.
- Administratively the NDA is complete and is being managed under “PDUFA V-The Program” until NDA 207561 (GENVOYA) is approved.
- The following changes were highlighted under PDUFA V:
 - Filing Letter - Date of the Internal MidCycle Meeting
 - Post-MidCycle Teleconference
 - Late-Cycle Meeting
- No Advisory Committee Meeting was scheduled.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM	Myung-Joo Patricia Hong	Y
	CPMS	Beth Thompson	Y
Cross-Discipline Team Leader (CDTL)	Islam Younis		Y
Division Director Deputy Director	Debra Birnkrant		N
	Jeff Murray		Y
Office Director/Deputy	Edward Cox/John Farley		N
Clinical	Reviewer:	Bill Tauber	Y
	Reviewer - Filing	Linda Lewis	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	Lisa Naeger	Y
	TL:	Jules O'Rear	Y
Clinical Pharmacology	Reviewer:	Mario Sampson	Y
	TL:	Islam Younis	Y
Biostatistics	Reviewer:	Tom Hammerstrom	Y
	TL:	Greg Soon	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Claudia Wrzesinski	Y
	TL:	Hanan Ghantous	N
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay)	Reviewer:	N/A	

validation) <i>(for protein/peptide products only)</i>	TL:	N/A	
	Reviewer:	Hari Sarker (DS) Suresh Pagay (DP)	N N
Product Quality (CMC)	TL:	Stephen Miller	Y
	Reviewer	Gerlie Gieser Elsbeth Chikhale	Y Y
Biopharmaceutics	TL:	Angelica Dorantes	N
	Reviewer:	N/A	
Quality Microbiology	TL:		
	Reviewer:		
CMC Labeling Review	TL:		
	Reviewer:		
Facility Review/Inspection	TL:		
	Reviewer:		
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Monica Calderon	Y
	TL:		
OSE/DRISK (REMS)	Reviewer:	Felicia Duffy	Y
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:	Tony El-Hage	N
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers/disciplines	Reviewer:	Sharon Mills - PLT Jessica Fox - OPDP	Y N
	TL:	Barbara Fuller - PLT	N
Other attendees	Stacey Min: ADL		Y
	Azeem D. Chaudhry: OSE RPM		Y
	Alexandra Bourgois: Pharmacy Intern		Y

	Moraine Le Bras: Pharmacy Intern	Y
	Elazhari Diae: Pharmacy Intern	Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain: NDA is reliant on BE to F/TAF component in E/C/F/TAF (NDA 207561). E/C/F/TAF clinical trials provide required efficacy/safety information and the clinical information is cross-referenced to NDA 207561.</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: This drug is not the first in its class

<ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>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</i> 	
<ul style="list-style-type: none"> ● 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? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> ● Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> ● Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES – BE sites inspection requested <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (protein/peptide products only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>New Molecular Entity (NDAs only)</p> <ul style="list-style-type: none"> • Is the product an NME? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><u>Quality Microbiology</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • 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? 	<input type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	<p>N/A</p>
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Debra Birnkrant, M.D.

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): September 17, 2015

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>

ACTIONS ITEMS

<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	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.
<input type="checkbox"/>	351(k) BLA/supplement: If filed, send filing notification letter on day 60
<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74

<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRA's 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/

MYUNG JOO P HONG
05/29/2015

ELIZABETH G THOMPSON
05/29/2015

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: 208215

Application Type: New NME NDA under "the Program"

Name of Drug/Dosage Form: DESCOVY (emtricitabine/tenofovir alafenamide fixed dose combination)
(F/TAF) 200/25 mg [REDACTED]^{(b) (4)} tablets

Applicant: Gilead Sciences, Inc.

Receipt Date: April 7, 2015

Goal Date: April 7, 2016

1. Regulatory History and Applicant's Main Proposals

DESCOVY is a two-drug fixed-dose combination (FDC) tablet consisting of emtricitabine and tenofovir alafenamide (F/TAF), both HIV nucleoside analog reverse transcriptase inhibitors (NRTIs), 200/ 25 mg [REDACTED]^{(b) (4)} tablets. GENVOYA (NDA 207561) is also under review by the Division in a new FDC (E/C/F/TAF) with a PDUFA goal date of November 5, 2015. If GENVOYA is approved, then DESCOVY will not be considered an NME at the time of its action. The original NDA was submitted on April 6, 2015 and received on April 7, 2015 and will be reviewed under a standard clock with a PDUFA goal date of April 7, 2016. The proposed indication for DESCOVY is for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older. DESCOVY has a prescribing information (PI) and patient package information (PPI).

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

No SRPI format deficiencies were identified in the review of this PI.

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.

Selected Requirements of Prescribing Information

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:

- YES** 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: HL are longer than one-half page but if "Boxed Warning" is removed, it should be one-half page.

- 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:

- YES** 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:

- YES** 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:

- 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.”)

Selected Requirements of Prescribing Information

• 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: *If GENVOYA is approved on 11/5/15 it is acceptable. If DESCOVY is approved before GENVOYA it will be 2016.*

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*.

Selected Requirements of Prescribing Information

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: Original NDA

- 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

- N/A** 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: Only tablet forms

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:

Selected Requirements of Prescribing Information

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:

Selected Requirements of Prescribing Information

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:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- 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:

Selected Requirements of Prescribing Information

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:

- YES** 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:

Selected Requirements of Prescribing Information

- 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

- YES** 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:

- N/A** 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:

(b) (4)

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

Selected Requirements of Prescribing Information

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:

Selected Requirements of Prescribing Information

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*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

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

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

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

/s/

MYUNG JOO P HONG
04/23/2015

ELIZABETH G THOMPSON
04/23/2015