CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208351Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 208351 SUPPL # HFD #

Trade Name ODEFSEY

Generic Name emtricitabine/rilpivirine/tenofovir alafenamide

Applicant Name Gilead Sciences, Inc.

Approval Date, If Known March 1, 2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The pivotal study to support approval was a BE/BA study entitled "A Phase 1, Randomized, Open-Label, Single-Dose, Three-Way, Six-Sequence, Cross-Over Stud 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)".

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

The remaining portion of the five-year NCE from the Genvoya application (NDA 207561) that was approved on November 5, 2015.

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 207561	GENVOYA
NDA# 202022	EDURANT
NDA# 202123	COMPLERA
NDA# 21500	EMTRIVA
NDA# 21896	EMTRIVA
NDA# 21752	TRUVADA
NDA# 203100	STRIBILD

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☒	NO ☐
Investigation #2	YES ☒	NO ☐
Investigation #3	YES ☒	NO ☐
Investigation #4	YES ☒	NO ☐
Investigation #5	YES ☒	NO ☐
Investigation #6	YES ☒	NO ☐

If you have answered "yes" for one or more investigations, identify each such

investigation and the NDA in which each was relied upon:

Investigation #1 GS-US-292-0104 NDA 207561
Investigation #2 GS-US-292-0111 NDA 207561
Investigation #3 GS-US-292-0109 NDA 207561
Investigation #4 GS-US-292-0112 NDA 207561
Investigation #5 GS-US-292-0106 NDA 207561

Investigation #6 TMC278-C213 NDA 202022/S-8

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form:
Title:
Date:

Name of Office/Division Director signing form:
Title:

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

CHRISTIAN P YODER
03/01/2016

JEFFREY S MURRAY
03/01/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 208351 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: ODESFEY Established/Proper Name: emtricitabine, rilpivirine, and tenofovir alafenamide Dosage Form: Tablet		Applicant: Gilead Sciences, Ind. Agent for Applicant (if applicable):
RPM: Christian Yoder		Division: DAVP

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is March 1, 2016	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments: **Tropical Disease Voucher used for priority review**

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action and date: Approval 3/1/2016
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included 7/1/2015
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included – bottle label 7/1/2015 and 2/22/2016
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	7/30/2015 7/24/2015
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ RPM-PLR Format Review 2/12/2016 DMEPA: ☒ 9/23/2015, 2/24/2016 DMPP/PLT (DRISK): ☒ 2/18/2016 OPDP: ☒ 2/22/2016 SEALD: ☐ None CSS: ☐ None Product Quality ☐ None Other: ☐ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	8/12/2015 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC January 6, 2016 If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☐ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg) May 22, 2015*	☒ 5/19/2015 - WRO
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg
• Mid-cycle Communication *(indicate date of mtg) October 8, 2015*	☒ 10/19/2015
• Late-cycle Meeting *(indicate date of mtg) December 11, 2015*	☒ 12/17//2015
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☒ None
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ 2/3/2016
PMR/PMC Development Templates *(indicate total number)*	☒ two
Clinical	

❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
• Clinical review(s) *(indicate date for each review)*	☒ 12/1/2015
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☐ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	☒ 2/3/2016
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☐ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☐ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☐ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☒ 12/2/2015
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☒ 12/1/2015
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ 1/5/2016

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☐ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☒ 11/23/2015
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☐ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☐ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☐ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☒ Review #1 – 12/4/2015 Review #2 – 2/3/2016
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☐ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	(included in Product Quality Discipline Reviews)
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☐ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☐ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	☐ Done

From:	Thompson, Elizabeth
To:	Patricia Carlos (Patricia.Carlos@gilead.com)
Cc:	Winestock, Karen; Yoder, Christian; Thompson, Elizabeth
Subject:	NDA 208351: Labeling comments
Date:	Monday, February 29, 2016 2:52:05 PM
Attachments:	2-29 proposed 8.1.docx
Importance:	High

Patricia-

I'm covering for Christian and Karen today. Attached please find additional comments for NDA 208351 for Odefsey (Section 8.1). If you agree with these changes, we will make them in the label that will be attached to the action letter. If you do not agree, please reply as soon as possible so that we can review.

Please let me know if you have any questions.

Regards,

Beth
Chief, Project Management Staff
FDA/CDER/OAP/DAVP
301-796-0824

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

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

/s/

ELIZABETH G THOMPSON
03/01/2016

Yoder, Christian

From: Patricia Carlos <Patricia.Carlos@gilead.com>
Sent: Monday, February 29, 2016 5:04 PM
To: Thompson, Elizabeth
Cc: Winestock, Karen; Yoder, Christian
Subject: RE: NDA 208351: Labeling comments

HI Beth;
We accept.
Thanks
Patricia

-----Original Message-----
From: Thompson, Elizabeth [mailto:Elizabeth.Thompson@fda.hhs.gov]
Sent: Monday, February 29, 2016 11:52 AM
To: Patricia Carlos
Cc: Winestock, Karen; Yoder, Christian; Thompson, Elizabeth
Subject: NDA 208351: Labeling comments
Importance: High

Patricia-

I'm covering for Christian and Karen today. Attached please find additional comments for NDA 208351 for Odefsey (Section 8.1). If you agree with these changes, we will make them in the label that will be attached to the action letter. If you do not agree, please reply as soon as possible so that we can review.

Please let me know if you have any questions.

Regards,

Beth
Chief, Project Management Staff
FDA/CDER/OAP/DAVP
301-796-0824

From:	Yoder, Christian
To:	"Patricia Carlos"
Cc:	Winestock, Karen
Subject:	NDA 208351 label changes
Date:	Thursday, February 25, 2016 3:30:00 PM
Attachments:	NDA 208351 draft-labeling-text-stk 2-25-16.docx NDA 208351 draft-labeling-text-stk 2-25-16.pdf

Hello Patricia,

Please see attached files with proposed labeling changes for NDA 208351 for Odefsey.

Please accept proposed changes where you agree and update the label with any further comments/changes and resubmit the label as soon as possible.

Please note that I will be out of the office on Friday and Monday, but will return on Tuesday. If you have any questions, please contact Karen Winestock.

Kind regards,

Christian

Christian P. Yoder, BSN, MPH
Regulatory Project Manager
Division of Antiviral Products (DAVP)
FDA/CDER/OND/OAP
White Oak Complex, Bldg. 22, Rm. 6317
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: (240) 402-9990 Fax: (301) 796-9883
Email: christian.yoder@fda.hhs.gov

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/s/

CHRISTIAN P YODER
02/25/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Naumann Chaudry, Pharm.D.
Director, Regulatory Affairs Advertising and Promotion
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

RE: NDA 208351
ODEFSEY® (emtricitabine, rilpivirine, and tenofovir alafenamide) Tablets
MA 1

Dear Dr. Chaudry:

This letter responds to Gilead Sciences, Inc.'s February 16, 2016, submission to the Office of Prescription Drug Promotion (OPDP) in accordance with 21 CFR 202.1(j)(4), requesting comments on a proposed core launch healthcare professional press release for ODEFSEY® (emtricitabine, rilpivirine, and tenofovir alafenamide) tablets, for oral use (Odefsey).

OPDP has reviewed the proposed press release. Based on a limited review of the information submitted, and our knowledge of the drug from premarket review, we offer the following comments, which we recommend be applied to this submission and to any other current and future promotional materials for Odefsey that contain the same or similar claims or presentations.

These comments are based on the draft product labeling (PI) for Odefsey included in your submission. We remind you that the press release, as well as future promotional materials, should be updated to reflect the final FDA-approved labeling.

(b) (4)

[redacted]

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/s/

JESSICA M FOX
02/25/2016

MEMORANDUM OF TELECONFERENCE

Teleconference Date: February 8, 2016

Application Number: NDA 208351
Product Name: Odefsey
Sponsor/Applicant Name: Gilead Sciences, Inc.

Subject: NDA 208351 labeling changes discussion

FDA Participants:
Islam Younis, Ph.D., Clinical Pharmacology Team Lead
Russell Fleischer, PA-C, MPH, Acting Clinical Team Lead
William Tauber, MD, Clinical Reviewer
Linda Lewis, MD, Clinical Reviewer
Stacey Min, MS, Associate Director for Labeling
Christian Yoder, Regulatory Project Manager
Karen Winestock, Chief, Project Management Staff
Elizabeth Thompson, Chief, Project Management Staff
Jeffrey Murray, MD, MPH, Deputy Director, DAVP
Debra Birnkrant, MD, Director, DAVP

Sponsor/Applicant Participants:
Andrew Cheng, MD PhD, Executive Vice President, HIV Therapeutics
Dana Pizzuti, MD Vice President, Regulatory Affairs
Christophe Beraud, PhD, Director, Regulatory Affairs
Erin Quirk, Sr. Director, HIV Therapeutics
Sonja Tong, MPH, Director, Regulatory Affairs Labeling
Patricia Carlos Manager, Regulatory Affairs

1.0 BACKGROUND: On February 4, 2016, the Division sent the sponsor their proposed labeling. On February 5, 2016, the sponsor requested a teleconference to discuss the Agency's labeling recommendations. On February 8, 2016, the sponsor sent a written summary with 4 items for discussion.

2.0 DISCUSSION:

Items for Discussion

1. **Indication Statement**

   The Agency has provided Gilead with a comment that the indication statement for F/R/TAF in virologically suppressed patients should be limited to patients that are on a ritonavir-boosted protease inhibitor based antiretroviral regimens. In light of the totality of the clinical data available in suppressed patients from Study GS-US-164-0106 and GS-

US-292-0109 submitted in the F/R/TAF NDA, the indication proposed by the Agency is unnecessarily restrictive. Gilead proposes the following indication:

(b) (4) is indicated as a complete regimen for the treatment of HIV-1 infection in patients 12 years of age and older:

- As initial therapy in those with no antiretroviral treatment history with HIV-1 RNA less than or equal to 100,000 copies per mL or
- To replace a stable (b) (4) antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) for at least six months with no history of treatment failure and no known substitutions associated with resistance to the individual components of (b) (4)

Per FDA guidance that the basis of approval should not be reflected in the Indication section of the label, the clinical studies providing the basis for the proposed indication will be described in Section 14-Clinical Studies of the USPI.

Meeting discussion:

The Division described the labeling process at the FDA as a dynamic one that evolves over time as we always leverage our knowledge and experience. The Division approach to Odefsey label is that the label should contain a summary of essential safety and efficacy information for use of the drug and these information should be contained directly in the label in order to meet the requirements at 21 CFR 201.56(a)(1). The Division does not believe that (b) (4)

The sponsor stated they believed the indication is unnecessarily restrictive and that the (b) (4) ***The Division responded that the proposed indication is consistent with the indication statement in Complera because there is no clinical data on Odefsey and approval is based on data from Complera and Genvoya. The sponsor agreed to propose new language for the indication.***

2. Presentation of Safety and Efficacy Data

Gilead acknowledges the Agency's addition of high level summaries in Section 6-Adverse Reactions and Section 14-Clinical Studies of the USPI (b) (4) . However, as proposed, (b) (4)

[redacted] As such, and in order to avoid a lengthy US PI, Gilead would like the discuss the possibility to [redacted]

Meeting discussion:

The sponsor asked if they could include [redacted]

The Division responded that we do not agree to [redacted] ***as this may be confusing to healthcare providers,*** [redacted]

The sponsor stated that they understood the Division's position.

3. **Changes made to form and presentation of USPI**

Gilead notes that there are inconsistencies in the presentation and structure of information in this USPI as compared to previously approved labels. Gilead would appreciate receiving confirmation from the Agency that that it intends to request future changes to [redacted]

Meeting discussion: There was no specific discussion on this point; see previous discussion.

4. **Request for Extension for Submission of Revised USPI**

Gilead requested an extension of the submission of the revised F/R/TAF and F/TAF USPIs to Thursday February 11, in order to have sufficient time to revise the labels based on the discussions with the Agency.

Meeting discussion: The Division agreed to the extension request to February 11.

3.0 ACTION ITEMS:

1. **The sponsor will propose new labeling language by February 11, 2016.**

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/s/

CHRISTIAN P YODER
02/23/2016

From:	Yoder, Christian
To:	"Patricia Carlos"
Subject:	NDA 208351 draft labeling changes
Date:	Friday, February 19, 2016 4:19:00 PM
Attachments:	NDA 208351 draft-labeling-text-stk 2-19-16.docx NDA 208351 draft-labeling-text-stk 2-19-16.pdf NDA 208351 PPI DMPP-OPDP Pt Info 2-19-16.docx

Hello Patricia,

Please see attached files with proposed labeling changes for NDA 208351 for Odefsey. Please note that the patient information is in a separate file.

Please accept proposed changes where you agree and update the label with any further comments/changes and resubmit the label no later than Tuesday, February 23, 2016.

Thank you very much,

Christian

Christian P. Yoder, BSN, MPH
Regulatory Project Manager
Division of Antiviral Products (DAVP)
FDA/CDER/OND/OAP
White Oak Complex, Bldg. 22, Rm. 6317
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: (240) 402-9990 Fax: (301) 796-9883
Email: christian.yoder@fda.hhs.gov

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/s/

CHRISTIAN P YODER
02/19/2016

From: Yoder, Christian
To: "Patricia Carlos"
Subject: RE: NDA 208351 bottle label
Date: Wednesday, February 17, 2016 4:00:00 PM

Hi Patricia,

1. We have only one additional comment for the bottle label. Can you please add the word "and" in the list of actives so it reads: "(emtricitabine, rilpivirine, and tenofovir alafenamide)"? Please make this correction and resubmit to the NDA. The is the only proposed change.
2. Yes, I hope to send you comments by Friday. If that isn't possible I will let you know.

Thanks,

Christian

From: Patricia Carlos [mailto:Patricia.Carlos@gilead.com]
Sent: Wednesday, February 17, 2016 12:30 PM
To: Yoder, Christian
Subject: NDA 208351
Importance: High

Hello Christian;
For planning purposes at Gilead, I have two quick questions regarding the F/R/TAF NDA ;

1. Can we expect any comments on the bottle label (Gilead wishes to begin printing)
2. Can we expect comments on the USPI this week as the PDUFA date is less than 2 weeks away

Thanks so much for your time.
Patricia

Patricia Carlos| Manager, Regulatory Affairs| Gilead Sciences, Inc.
☎ (650) 372-7621 | ✉ patricia.carlos@gilead.com

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/s/

CHRISTIAN P YODER
02/17/2016

From: Yoder, Christian
To: "Patricia Carlos"
Subject: NDA 208351 draft labeling changes
Date: Thursday, February 04, 2016 3:03:00 PM
Attachments: NDA 208351 draft-labeling-text-stk 2-4-16 Rev.docx
NDA 208351 draft-labeling-text-stk 2-4-16 Rev.pdf

Hello Patricia,

Please see attached files with proposed labeling changes for NDA 208351 for Odefsey.

Please note these additional comments:

The Division acknowledges the advice communicated to the Sponsor on 6/23/2015. Upon further consideration and internal discussion, we do not agree with your proposals for Sections 6 and 14. (b) (4) for the following reasons:

(b) (4)

Please see the current Division recommendations for meeting this requirement in FDA comments contained in Sections 6 and 14 of the ODEFSEY labeling (Division communication dated 1/14/2016).

Please accept proposed changes where you agree and update the label with any further comments/changes and resubmit the label no later than Tuesday, February 9, 2016.

Thank you very much,

Christian

Christian P. Yoder, BSN, MPH
Regulatory Project Manager
Division of Antiviral Products (DAVP)
FDA/CDER/OND/OAP
White Oak Complex, Bldg. 22, Rm. 6317
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: (240) 402-9990 Fax: (301) 796-9883

Email: christian.yoder@fda.hhs.gov

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CHRISTIAN P YODER
02/04/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: **208351**

Drug: **emtricitabine/rilpiverine/tenofovir alafenamide**

Date: **January 29, 2016**

To: **Ms. Patricia Carlos, Manager, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

Subject: **NDA 208351 Information request**

We are reviewing the labeling provided in your January 22, 2016 submission for ODEFSEY (NDA 208351) and have the following comments and information request. We acknowledge that the proposed labeling is in the requested format and structure of the Pregnancy and Lactation Labeling Rule (PLLR) (79 FR 72064); however, during our review of your submitted labeling, we found that you have not provided adequate information to support the labeling content for subsection 8.1, specifically the human safety data. Thus, your proposed PLLR labeling changes cannot be agreed upon until this information request is fulfilled. No partial PLLR conversions may be made.

Submit the following by February 5, 2016:

- a review and summary of the available published literature regarding emtricitabine use in pregnant and lactating women
- a review and summary of the available published literature regarding rilpivirine use in pregnant and lactating women
- a review and summary of relevant cases reported in your pharmacovigilance database
- an interim report of an ongoing pregnancy registry, in this case, the Antiretroviral Pregnancy Registry
- revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.

Refer to the Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf). Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via email for your convenience. Please feel free to contact me at (240) 402-9990 if you have any questions regarding the contents of this transmission.

Christian P. Yoder, BSN, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
01/29/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: **208351**

Drug: **emtricitabine/rilpiverine/tenofovir alafenamide**

Date: **January 21, 2016**

To: **Ms. Patricia Carlos, Manager, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

Subject: **NDA 208351 Information request**

Please refer to your New Drug Application that was received on July 1, 2015. We have the following request for information:

1. Please describe the reason(s) for including "Dispense in original container" in the Prescribing Info for the product currently under review in NDA 208351.

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via email for your convenience. Please feel free to contact me at (240) 402-9990 if you have any questions regarding the contents of this transmission.

Christian P. Yoder, BSN, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
01/21/2016

From:	Yoder, Christian
To:	"Patricia Carlos"
Subject:	NDA 208351 label
Date:	Thursday, January 14, 2016 3:11:00 PM
Attachments:	NDA 208351 draft-labeling-text-stk 1-14-16.docx NDA 208351 draft-labeling-text-stk 1-14-16.pdf

Hello Patricia,

Please see attached files with proposed labeling changes for NDA 208351 for Odefsey.

Please note, according to 21 CFR 201.56, the labeling must contain a summary of the essential scientific information needed for the effective use of ODEFSEY. Therefore, we recommend including a summary of the description and results of the important trials that support the efficacy of FTC and TAF in HIV-1. We also recommend (b) (4) (b) (4)).

Please accept proposed changes where you agree and update the label with any further comments/changes and resubmit the label no later than Friday, January 22, 2016.

Thanks,

Christian

Christian P. Yoder, BSN, MPH
Regulatory Project Manager
Division of Antiviral Products (DAVP)
FDA/CDER/OND/OAP
White Oak Complex, Bldg. 22, Rm. 6317
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: (240) 402-9990 Fax: (301) 796-9883
Email: christian.yoder@fda.hhs.gov

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/s/

CHRISTIAN P YODER
01/14/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208351

INFORMATION REQUEST

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 and received July 1, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for emtricitabine, rilpivirine, and tenofovir alafenamide tablets.

We also refer to the T-con meeting held on December 3, 2015 and the late cycle T-con meeting on December 11, 2015, discussing the dissolution acceptance criteria.

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

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

We request that you respond by indicating your preference between these two options by January 6, 2016.

If you have questions, call me at (240) 402-2691.

Sincerely,
Bamidele F. Aisida -A

D gitally signed by Bamidele F Aisida A
DN:c US o U S Government ou HHS ou FDA ou People 0 9 2342 19200300 100 1 1 2001703308 cn Bamidele F Aisida A
Date: 2015 12 17 16:04 03 05'00'

Florence Aisida, Pharm.D, BCPS
Regulatory Business Process Manager
Office of Program and Regulatory Operations

Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208351

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 July 1, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for emtricitabine/rilpivirine/tenofovir alafenamide fixed dose combination, 200/25/25 mg.

We also refer to our August 25, 2015, letter in which we notified you of our target date of December 3, 2015, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals and Procedures - Fiscal Years 2013 Through 2017."

We have the following proposed PREA postmarketing requirement. Please note that exact language will be determined following consultation with the Pediatric Review Committee.

Using data from agreed upon studies of the component products, conduct and submit an assessment of safety, pharmacokinetics, and antiviral activity of RPV/F/TAF in pediatric patients 6 years to less than 12 years of age OR greater than 25kg.

Please provide confirmation of milestone dates:

Protocol Submission – completed
Study Completion –
Study Submission –

If you have any questions, call Christian Yoder, Regulatory Project Manager, at (240) 402-9990.

Sincerely,

{See appended electronic signature page}

Christian P. Yoder, BSN, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
12/03/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: **208351**

Drug: **emtricitabine/rilpiverine/tenofovir alafenamide**

Date: **December 1, 2015**

To: **Ms. Patricia Carlos, Manager, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

Subject: **NDA 208351 Information request**

Please refer to your New Drug Application that was received on July 1, 2015. Please see the following comment, and respond by December 4, 2015:

1. Please provide a link to or submit the full method validation report corresponding to partial validation report SH08-J01-TR288/BA1099.

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via email for your convenience. Please feel free to contact me at (240) 402-9990 if you have any questions regarding the contents of this transmission.

Christian P. Yoder, BSN, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
12/01/2015

From:	Aisida, Bamidele (Florence)
To:	"Patricia Carlos"
Cc:	Yoder, Christian
Subject:	NDA 208351 IR
Date:	Monday, November 23, 2015 9:07:17 AM

Hello Patricia,

We are reviewing the Chemistry Manufacturing and Controls section of your submission and have the following information request. We request a written response in order to continue our evaluation of your NDA by Monday Nov 30, 2015 (COB, PST).

The provided dissolution data support a dissolution acceptance criterion of Q= (b) (4) *% at* (b) (4) *minutes for Emtricitabine (FTC) and Tenofovir Alafenamide (TAF). The provided dissolution data also support a dissolution acceptance criterion of Q=* (b) (4) *% at 30 minutes for Rilpivirine (RPV). Note that the dissolution testing may require stage 2 testing and occasionally stage 3 testing. Provide a revised drug product specification table and update your stability protocol accordingly.*

Please confirm receipt of this email.

If I can provide you with any further information, please let me know.

Thanks,

Florence Aisida, Pharm.D,BCPS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (240) 402-2691
Email: bamidele.aisida@fda.hhs.gov

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: **208351**

Drug: **emtricitabine/rilpiverine/tenofovir alafenamide**

Date: **November 18, 2015**

To: **Ms. Patricia Carlos, Manager, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

Subject: **NDA 208351 Information request**

Please refer to your New Drug Application that was received on July 1, 2015. Please see the following comment, and respond by November 25, 2015:

1. Provide a link to or submit the following bioanalytical reports: (b) (4) 42-1102, (b) (4) 60-1277, (b) (4) 42-1222, (b) (4) 86-0938, and SH08-J01-TR288/BA1099.

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via email for your convenience. Please feel free to contact me at (240) 402-9990 if you have any questions regarding the contents of this transmission.

Christian P. Yoder, BSN, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
11/18/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208351

INFORMATION REQUEST

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 and received July 1, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for FTC/RPV/TAF (emtricitabine/rilpivirine/tenofovir alafenamide) Tablets.

We are reviewing the Chemistry Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response in order to continue our evaluation of your NDA by Nov 13, 2015.

1. Regarding the acceptance criterion for the (b) (4) of the tablets the information that you supplied in your Amendment of 10/16/15 was helpful but a limit of NMT (b) (4)% still gives us some concern.

   You provided batch release data for 12 batches that have a (b) (4) of (b) (4)% and there is no obvious trend (b) (4) on stability, indeed there is an initial (b) (4) (b) (4) Clearly your manufacturing process and container-closure system can maintain the (b) (4) in the (b) (4)% range.

   (b) (4)

   Please (b) (4) the acceptance criterion for (b) (4) to NMT (b) (4)%.

2. [redacted] Finally, please provide a protocol that details all your current plans for performing process validation.

3. Since protection from [redacted] is important for this product, the [redacted] of in-process materials should be consistent across manufacturing sites. It is noted in batch records terms like [redacted] are sometimes used to describe [redacted] Please specify the [redacted] configurations that will be used for in-process materials such as [redacted] during commercial production. For example, a typical configuration for such materials might be the use of [redacted] Please also clarify [redacted] Finally, please confirm that the [redacted] configurations will be consistent with those used in [redacted] studies that are being used to justify [redacted]

If you have questions, call me at (240) 402-2691.

Sincerely,

Bamidele F. Aisida -A

Digitally signed by Bamidele F. Aisida -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001703398, cn=Bamidele F. Aisida -A
Date: 2015.10.30 14:43:19 -04'00'

Florence Aisida, Pharm.D, BCPS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208351

MID-CYCLE COMMUNICATION

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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Odefsey (emtricitabine/rilpivirine/tenofovir alafenamide) fixed dose combination tablet 200/25/25 mg.

We also refer to the teleconference between representatives of your firm and the FDA on October 8, 2015. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me, Christian P. Yoder, Regulatory Project Manager at (240) 402-9990.

Sincerely,

{See appended electronic signature page}

Christian P. Yoder, BSN, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: October 8, 2015, 2:00 pm

Application Number: NDA 208351
Product Name: Odefsey (emtricitabine/rilpivirine/tenofovir alafenamide)
Indication: For the treatment of HIV-1 infection
Applicant Name: Gilead Sciences, Inc.

Meeting Chair: Islam Younis, Ph.D.
Meeting Recorder: Christian P. Yoder, BSN, MPH

FDA ATTENDEES:

Office of Antimicrobial Products

Debra Birnkrant, M.D., Director, Division of Antiviral Products
Jeffrey Murray, M.D., Deputy Director, Division of Antiviral Products
Russ Fleischer, PA-C, MPH, Acting Clinical Team Leader, Division of Antiviral Products
Jules O'Rear, Ph.D., Clinical Virology Team Leader, Division of Antiviral Products
Karen Winestock, Chief, Project Management Staff, Division of Antiviral Products

Office of Clinical Pharmacology

Islam Younis, Ph.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology IV
Jason Xu, Pharmacy Student

Office of Pharmaceutical Quality

Stephen Miller, Ph.D., Product Quality CMC-Lead
Om Anand, Ph.D., Biopharmaceutics Reviewer

Office of Surveillance and Epidemiology
Monica Calderon, Pharm.D., BCPS, DMEPA Reviewer

Eastern Research Group Participants

Marc Goldstein, Independent Assessor

APPLICANT ATTENDEES:

Dana Pizzuti, M.D., Vice President, Regulatory Affairs
Brian Kearney, Pharm.D., Vice President, Clinical Pharmacology
Erin Quirk, M.D., Senior Director, Clinical Research
Monica Tijerina, Director, Formulation Process Development
Julia Zack, Senior Clinical Pharmacologist, Clinical Pharmacology
Patricia Carlos, Manager, Regulatory Affairs
Stephani Berger, Senior Manager, Regulatory Affairs, CMC

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

No significant issues have been identified to date.

3.0 INFORMATION REQUESTS

Product Quality
The Division noted that an Information Request letter was sent on October 2, 2015, and Gilead indicated that responses are currently being prepared. No further discussion occurred.

Content of October 2, 2015, IR letter, for reference:

1. Regarding the acceptance criterion for the (b) (4) of the tablets the information that you supplied in your Amendment of 9/24/15 clearly shows that (b) (4)
(b) (4)

(b) (4)

2. Regarding your agreement in the Amendment of 9/24/15 to evaluate particle size of the (b) (4) as well as perform dissolution testing of the tablets during process validation, please update section 3.2.P.3.5 Process Validation and/or Evaluation [F/R/TAF Tablets] accordingly.

3. Provide a list of critical material attributes (CMA) and critical process parameters (CPP) affecting dissolution. Demonstrate that your proposed dissolution methods are discriminating with regard to the CMAs and CPPs.

4. Module 3.2.P.5.2, [Discriminatory Capability of Dissolution Method] stated that discriminatory capacity of the dissolution method was established through evaluation

(b) (4)

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology do not believe a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks.

5.0 ADVISORY COMMITTEE MEETING

No Advisory Committee Meeting is scheduled for this application.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The Late Cycle Meeting (LCM) is scheduled for December 11, 2015. The purpose of the LCM is to share information and discuss any review issues identified to date, as well as objectives for the remainder of the review cycle. The Division will send the meeting backgrounder package for the LCM by secure electronic mail by November 30, 2015.

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/s/

CHRISTIAN P YODER
10/19/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208351

INFORMATION REQUEST

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

Dear Mr. Carlos:

Please refer to your New Drug Application (NDA) dated and received July 1, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for FTC/RPV/TAF (emtricitabine/rilpivirine/tenofovir alafenamide) Tablets.

We are reviewing the Chemistry Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response in order to continue our evaluation of your NDA by October 16, 2015.

1. Regarding the acceptance criterion for the (b) (4) of the tablets the information that you supplied in your Amendment of 9/24/15 clearly shows that (b) (4)
(b) (4)

(b) (4)

2. Regarding your agreement in the Amendment of 9/24/15 to evaluate particle size of the (b) (4) as well as perform dissolution testing of the tablets during process validation, please update section 3.2.P.3.5 Process Validation and/or Evaluation [F/R/TAF Tablets] accordingly.

3. Provide a list of critical material attributes (CMA) and critical process parameters (CPP) affecting dissolution. Demonstrate that your proposed dissolution methods are discriminating with regard to the CMAs and CPPs.

4. Module 3.2.P.5.2, [Discriminatory Capability of Dissolution Method] stated that discriminatory capacity of the dissolution method was established through evaluation (b) (4)

(b) (4)

(b) (4)

If you have questions, call me at (240) 402-2691.

Sincerely,

Bamidele F. Aisida -A

Digitally signed by Bamidele F. Aisida -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001703308, cn=Bamidele F. Aisida -A
Date: 2015.10.02 13:55:56 -04'00'

Florence Aisida, Pharm.D, BCPS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208351

INFORMATION REQUEST

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 and received July 1, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for FTC/RPV/TAF (emtricitabine/rilpivirine/tenofovir alafenamide) tablets.

We are reviewing the Chemistry Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response in order to continue our evaluation of your NDA by **September 24, 2015.**

1. Some excipients, e.g., lactose monohydrate, microcrystalline cellulose, povidone, can be obtained in a variety of grades that vary in such parameters as particle size, (b) (4), and viscosity. Please specify which grade of each excipient is used in the manufacturing process or provide evidence to show that the quality of the product is not influenced by the grade of excipient that is used.

2. We note that the (b) (4) for tablets in the container-closure system is (b) (4)%. (b) (4). Given the risk of tenofovir alafenamide (b) (4) we recommend that you (b) (4)%.

3. Please provide a justification for not providing a drug product test for heavy metals.

4. Please indicate when a drug product stability update might be expected.

5. Please indicate when the expiration dating period is considered to begin.

6. (b) (4)

(b) (4) You may also propose future studies or provide justification for not performing this type of evaluation.

7. We note that in 3.2.P.3.3 (Operating Parameters 1.4.1), that there are differences in operating parameters between batches manufactured at (b) (4) (b) (4). Please provide a comparative listing of the equipment (type, manufacturer, model #, working capacity, etc.) to be used at each site, along with explanation for the differences in operating parameters.

8. For Process Validation and/or Evaluation of F/R/TAF tablets, 3.2.P.3.5- it is noted that particle size analysis of the (b) (4) as well as dissolution testing of the tablets are not proposed as part of the protocol. It is recommended that these key product attributes be evaluated, or justification provided for their exclusion.

9. In Regional Information 3.2.R you provided executed batch records for a representative batch manufactured at (b) (4). Please also provide executed batch records for a representative batch manufactured at (b) (4)

10. (b) (4)

If you have any questions, call Florence Aisida, Regulatory Process business Manager, at (240) 402-2691.

Sincerely,

Stephen Miller -S

Digitally signed by Stephen Miller -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Stephen Miller -S, 0.9.2342.19200300.100.1.1=1300087013
Date: 2015.09.10 09:41:34 -04'00'

Stephen Miller, Ph.D
On Behalf of
Balajee Shanmugam, Ph.D.
Branch Chief, Branch III (Acting)
Division of New Drug Products 1
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208351

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

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 July 1, 2015, received July 1, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for emtricitabine/rilpivirine/tenofovir alfenamide fixed dose combination tablet, 200/25/ (b) (4) mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a) this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority** because you submitted a Tropical Diseases voucher. Therefore, the user fee goal date is March 1, 2016. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.)

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by December 3, 2015.

In addition, the planned date for our internal mid-cycle review meeting is September 29, 2015. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

Clinical Pharmacology

1. Essential information for study TMC278-TiDP6-C154 was not provided in the submission. Please submit datasets and bioanalytical method validation reports for study TMC278-TiDP6-C154.

We are providing the above comment to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following clinical pharmacology information on or before September 4, 2015:

1. Please submit datasets and bioanalytical method validation reports for study TMC278-TiDP6-C154.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances, and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

1. Under Highlights of Prescribing Information, there should be white spacing after the "Initial U.S. Approval: YYYY and above the INDICATIONS AND USAGE section. The white space under the DRUG INTERACTIONS and the USE IN SPECIFIC POPULATIONS sections should be deleted.

2. In the INDICATIONS AND USAGE section, there are no references given for two paragraphs under the subsection "Limitations of Use," and in the first bullet under the DRUG INTERACTIONS section.
3. In the Table of Contents, in 6.2, "Post Marketing" is written as two words but in the Full Prescribing Information (FPI) it is written as one word, "Postmarketing."
4. In subsection 12.3 of the FPI, Pharmacokinetics, under the "Pediatric Patients" heading, the parentheses are missing around "8.4" in the reference: "[See Use In Specific Populations 8.4]"

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by September 8, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

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

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for (b) (4) to (b) (4) less than 6 years of age in this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for children 6 years to less than 12 years in this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

We note that you have submitted pediatric studies with this application for pediatric patients 12 years to less than 18 years. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this age group.

If you have any questions, call Christian Yoder, Regulatory Project Manager, at (240) 402-9990.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antiviral Products
Office of Drug Evaluation Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

JEFFREY S MURRAY
08/25/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 208351

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

ATTENTION: Patricia Carlos
Manager, Regulatory Affairs

Dear Ms. Carlos:

Please refer to your New Drug Application (NDA) dated and received July 1, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Emtricitabine, Rilpivirine, Tenofovir Alafenamide Tablets, 200 mg/25 mg/25 mg.

We also refer to your correspondence dated and received July 2, 2015, requesting review of your proposed proprietary name, Odefsey. We have completed our review of the proposed proprietary name Odefsey, and have concluded it is conditionally acceptable.

If any of the proposed product characteristics as stated in your July 2, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3813. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager Christian Yoder, at (240) 402-9990.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

AZEEM D CHAUDHRY
07/30/2015

TODD D BRIDGES
07/30/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: **208351**

Drug: **emtricitabine/rilpiverine/tenofovir alafenamide**

Date: **July 30, 2015**

To: **Ms. Patricia Carlos, Manager, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc.**

Subject: **NDA 208351 Information request**

Please refer to your New Drug Application that was received on July 1, 2015. Please see the following comments, and respond by August 14:

1. Please provide a timetable showing when stability data on [redacted] (b) (4) will be available for submission.

2. Please submit Letters of Authorization to Gilead's NDA 21752 and NDA 207561, to allow FDA review of information on Emtricitabine and TAF fumarate, beyond what is included by cross-application links, in support of NDA 208351.

PLEASE REPLY BY EMAIL (christian.yoder@fda.hhs.gov) to confirm receipt. We are providing this above information via email for your convenience. Please feel free to contact me at (240) 402-9990 if you have any questions regarding the contents of this transmission.

Christian P. Yoder, BSN, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTIAN P YODER
07/30/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208351

NDA ACKNOWLEDGMENT

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

Dear Ms. Carlos:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: emtricitabine/rilpivirine/tenofovir alafenamide fixed dose combination 200/25/25 mg

Date of Application: July 1, 2015

Date of Receipt: July 1, 2015

Our Reference Number: NDA 208351

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 30, 2015, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Christian Yoder, Regulatory Project Manager, at (240) 402-9990 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Christian P. Yoder, BSN, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

CHRISTIAN P YODER
07/06/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 123098

MEETING PRELIMINARY COMMENTS

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

Dear Ms. Carlos:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for emtricitabine, rilpivirine, and tenofovir alafenamide (FTC/RPV/TAF) fixed-dose combination tablets.

We also refer to your March 19, 2015, correspondence, received March 19, 2015 requesting a teleconference to discuss the content and format of your planned New Drug Application (NDA), as well as your safety update proposal.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (301) 796-0824.

Sincerely,

{See appended electronic signature page}

Elizabeth Thompson, M.S.
Chief, Project Management Staff
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: May 22, 2015 2:00 – 3:00 PM EDT
Meeting Location: Teleconference

Application Number: IND 123098
Product Name: emtricitabine, rilpivirine, and tenofovir alafenamide tablets
Indication: treatment of HIV-1 infection
Sponsor/Applicant Name: Gilead Sciences, Inc.

FDA ATTENDEES (tentative)

Office of Antimicrobial Products
- Edward Cox, Office Director
- John Farley, Deputy Office Director

Division of Antiviral Products
- Jeffrey Murray, Deputy Director
- Linda Lewis, Clinical Team Leader
- Jules O'Rear, Clinical Virology Team Leader
- Lisa Naeger, Clinical Virology Reviewer
- Hanan Ghantous, Pharmacology/Toxicology Team Leader
- Claudia Wrzesinski, Pharmacology/Toxicology Reviewer
- Elizabeth Thompson, Chief, Project Management Staff

Office of Clinical Pharmacology
- Islam Younis, Clinical Pharmacology Team Leader
- Mario Sampson, Clinical Pharmacology Reviewer

Office of Product Quality
- Stephen Miller, CMC-Lead
- Olga Simakova, Regulatory Business Process Manager
- Angelica Dorantes, Acting Biopharmaceutics Branch Chief
- Elsbeth Chikhale, Acting Biopharmaceutics Team Lead
- Banu Zolnik, Biopharmaceutics Reviewer

SPONSOR ATTENDEES (Gilead Sciences, Inc.)

Andrew Cheng, MD, PhD, Executive Vice President, HIV Therapeutics and Development Operations
Erin Quirk, MD, Senior Director, Clinical Research
Christophe Beraud, PhD, Director, Regulatory Affairs
Patricia Carlos, Manager, Regulatory Affairs
Brian Kearney, PharmD, Vice President, Clinical Pharmacology
Julia Zack, PharmD, Director, Clinical Pharmacology
Stephani Berger, Senior Manager, Regulatory Affairs, CMC

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for May 22, 2015 between Gilead Sciences, Inc. and the Division of Antiviral Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Gilead Sciences, Inc. is developing the fixed-dose combination of emtricitabine, rilpivirine and tenofovir alafenamide tablets (FTC/RPV/TAF) for the treatment of HIV-1 infection in (b) (4) (b) (4) patients 12 years of age and older. Gilead plans to submit an NDA for approval of FTC/RPV/TAF tablets on the basis of bioequivalence (BE) trial GS-US-366-1159, comparing it to the following reference products:

- EVG/COBI/FTC/TAF (elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide) fixed-dose combination tablets (NDA 207561 currently under review)
- EDURANT (rilpivirine) tablets

On February 17, 2015, the Agency provided feedback to Gilead agreeing that the fed BE study GS-US-366-1159 and food effect study GS-US-366-1159 would be sufficient to support submission of an NDA for FTC/RPV/TAF without the need for BE data in the fasted stated.

On March 17, 2015, Gilead informed the Agency of its intention to use a Tropical Disease Priority Review Voucher for the FTC/RPV/TAF NDA (NDA 208215), to be submitted on July 1, 2015.

On March 19, 2015 Gilead requested a pre-NDA teleconference to discuss the content and structure of the planned NDA, a proposal for the NDA safety update, and the target product labeling.

2.0 DISCUSSION

Questions from Gilead Sciences are shown below in ***bold, italicized*** font and responses from DAVP are shown in standard font.

Question 1:
Does the Agency have any comments on the proposed draft NDA table of contents?

FDA Response to Question 1***:***
The proposed TOC is acceptable. Please add FTC/RPV/TAF food effect study GS-US-366-1651 to the table of contents.

Question 2:
Does the Agency agree with the proposal to cross-reference previously submitted nonclinical and clinical study reports to their respective NDAs?

FDA Response to Question 2:
Your proposal to cross-reference previously submitted clinical and non-clinical study reports is acceptable.

Question 3:
Does the Agency agree with the proposal to cross reference FTC and TAF drug substance information via cross-application links in section 3.2.S?

FDA Response to Question 3:
Your proposal is acceptable.

Question 4:
Does the Agency agree with the proposal to provide a cross reference leaf to the E/C/F/TAF nonclinical written and tabulated summaries for information related to FTC and TAF in the FTC/RPV/TAF FDC NDA?

FDA Response to Question 4:
We agree with your approach. However, please include a specific risk analysis of the synergistic and additive toxicity potentials for this specific combination product in your submission.

Question 5:
Does the Agency agree with the proposal to cross-reference the F/TAF NDA Safety Update in lieu of the submission of a NDA Safety Update for the FTC/RPV/TAF NDA?

FDA Response to Question 5:
Your proposal to cross-reference the Safety Update for NDA 208215 is acceptable

Question 6:
Does the Agency agree with the proposal to submit investigator financial information only for Study GS-US-366-1159?

FDA Response to Question 6:
Your proposal is acceptable. However, if the covered studies for NDA 207561 for Genvoya are found to be biased secondary to financial interests, it may impact this application.

Question 7a:
Does the Agency agree with the proposed indication for the treatment of HIV-1 infection in (b) (4) patients 12 years and older with (b) (4) no antiretroviral treatment history or who are virologically suppressed to replace (b) (4) regimen?

FDA Response to Question 7a:
The labeled indication for this product will be a review issue and will be dependent on approvals of the Genvoya NDA and the supplemental NDA for rilpivirine in adolescents.

Question 7b:
Does the Agency have any other comments on the TPL?

FDA Response to Question 7b:
The content of the label will be a review issue. However, according to the *Guidance for Industry, Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products- Content and Format,* the Clinical Studies section should include studies that provide primary support for effectiveness. Since there was no efficacy study conducted with F/TAF, the data proposed in Section 14 of the TPL does not belong in this labeling. Please refer to (b) (4) and EVOTAZ label for examples.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our March 31, 2015 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

4.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge your Agreed iPSP submitted on April 23, 2015. Your Agreed iPSP, along with any requests for waivers or deferrals, should be included in your New Drug Application.

5.0 PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in 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 42 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.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

6.0 MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

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/s/

ELIZABETH G THOMPSON
05/19/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208351

LATE-CYCLE MEETING MINUTES

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 July 1, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Odefsey (emtricitabine, rilpivirine, and tenofovir alafenamide) fixed dose combination tablet 200/25/25 mg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on December 11, 2015.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Christian Yoder, Regulatory Project Manager at (240) 402-9990.

Sincerely,

{See appended electronic signature page}

Islam Younis, Ph.D.
Cross Discipline Team Lead
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: December 11, 2015, 2:30 p.m.
Meeting Location: Teleconference

Application Number: NDA 208351
Product Name: Odefsey (emtricitabine, rilpivirine, and tenofovir alafenamide)
Applicant Name: Gilead Sciences, Inc.

Meeting Chair: Islam Younis, Ph.D.
Meeting Recorder: Christian Yoder, BSN, MPH

FDA ATTENDEES

Office of Antimicrobial Products

Debra Birnkrant, M.D., Director, Division of Antiviral Products
Jeffrey Murray, M.D., Deputy Director, Division of Antiviral Products
William Tauber, M.D. Medical Officer, Division of Antiviral Products
Lisa Naeger, Ph.D., Virology Reviewer, Division of Antiviral Products
Stacey Min, Pharm.D., Associate Director for Labeling, Division of Antiviral Products
Sohail Mosaddegh, Pharm.D., Regulatory Project Manager, Division of Antiviral Products

Office of Clinical Pharmacology

Islam Younis, Ph.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology IV

Office of Pharmaceutical Quality

Stephen Miller, Ph.D., Product Quality CMC-Lead
Om Anand, Ph.D., Biopharmaceutics Reviewer
Rose Xu, M.Sc., Microbiologist/Compliance Officer

EASTERN RESEARCH GROUP ATTENDEES

Peggah Khorrami, Independent Assessor

APPLICANT ATTENDEES

Andrew Cheng, Executive Vice President, Clinical Research and Development Operations
Reza Oliyai, Vice President, Product Development and Clinical Supplies
Dana Pizzuti, M.D., Vice President, Regulatory Affairs

Brian Kearney, Pharm.D., Vice President, Clinical Pharmacology
Erin Quirk, M.D., Senior Director, Clinical Research
Monica Tijerina, Director, Formulation Process Development
Julia Zack, Senior Clinical Pharmacologist, Clinical Pharmacology
Patricia Carlos, Manager, Regulatory Affairs
Erik Berglund M.D. Associate Director, Regulatory Affairs
Stephani Berger, Senior Manager, Regulatory Affairs, CMC

1.0 BACKGROUND

NDA 208351 was submitted on July 1, 2015, for Odefsey (emtricitabine, rilpivirine, and tenofovir alafenamide).

Proposed indication(s): For the treatment of HIV-1 infection

PDUFA goal date: March 1, 2015

FDA issued a Background Package in preparation for this meeting on November 30, 2015.

2.0 DISCUSSION

1. Introductory Comments

Discussion:

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package, we may not be prepared to discuss that new information at this time.

2. Information Requests

Discussion:

Clinical Pharmacology:

The information request has been addressed and there are no further requests at this time.

Product Quality:

From the Product Quality perspective there are two review issues that are still under review:

1. Drug Substance (DS), DP, and process reviews are complete, and there are no outstanding issues with these reviews.
    - The evaluation of inspection results from all manufacturing, testing and packaging facilities has not yet been completed.
    - We have some advice comments relating to (b) (4) Process Verification, which we will send out an advice letter after the LCM. They are not approvability issues.

2. After the t-con with Gilead on Thursday, December 3, 2015, we had further discussions to consider Q= (b) (4)% at the two possible regulatory time points for the rilpivirine dissolution test. We believe the data support the 30-minute time point rather than the 45-minute time point. We see two possible approaches to resolve this issue:
    a. agreement to use Q= (b) (4)% at the 30-min time point for the regulatory specification, or
    b. establishment of an interim specification with Q= (b) (4)% at the 45-min time point, with a Post-Marketing Commitment to compare results at the 30- and 45-min times after a sufficient amount of commercial manufacturing experience has been gained.

    FDA will send an Information Request letter to Gilead to provide these two options in writing after the Late Cycle meeting.

3. Postmarketing Requirements/Postmarketing Commitments

Discussion:

As this NDA triggers PREA, pediatric studies will be required as PREA PMRs. These PMRs will reflect studies outlined in your Agreed iPSP.

4. Major Labeling Issues

Discussion:

The labeling review is ongoing and the Division anticipates sending a draft labeling to Gilead the second week of January.

5. Review Plans – There was no discussion.

6. Wrap-up and Action Items

- FDA will send draft labeling comments to Gilead the second week of January 2016.

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/s/

ISLAM R YOUNIS
12/17/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208351

LATE CYCLE MEETING
BACKGROUND PACKAGE

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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Odefsey (emtricitabine/rilpivirine/tenofovir alafenamide) fixed dose combination tablet 200/25/25 mg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for December 11, 2015. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Christian Yoder, Regulatory Project Manager, at (240) 402-9990.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: December 11, 2015, 2:30 p.m. – 3:30 p.m.
Meeting Location: Teleconference

Application Number: NDA 208351
Product Name: Odefsey (emtricitabine/rilpivirine/tenofovir alafenamide)
Indication: For the treatment of HIV-1 infection
Sponsor/Applicant Name: Gilead Sciences, Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. **Discipline Review Letters**

   No Discipline Review letters have been issued to date.

2. **Substantive Review Issues**

   There are no substantive review issues at this time.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes (Christian Yoder, Regulatory Project Manager, Islam Younis, Cross Discipline Team Lead)

   Welcome, Introductions, Objectives of the meeting

2. Information Requests – 5 minutes

   Clinical Pharmacology

   Request sent November 18, 2015: Provide a link to or submit the following bioanalytical reports: (b) (4) 42-1102, (b) (4) 60-1277, (b) (4) 42-1222, (b) (4) 86-0938, and SH08-J01-TR288/BA1099.

   Chemistry, Manufacturing, and Controls

   a. Request sent November 23, 2015: The provided dissolution data support a dissolution acceptance criterion of Q= (b) (4)% at (b) (4) minutes for Emtricitabine (FTC) and Tenofovir Alafenamide (TAF). The provided dissolution data also support a dissolution acceptance criterion of Q= (b) (4)% at 30 minutes for Rilpivirine (RPV). Note that the dissolution testing may require stage 2 testing and occasionally stage 3 testing. Provide a revised drug product specification table and update your stability protocol accordingly.
   b. Regarding the stability data for drug product batches EF1403B1 and EF1404B1, we request that Gilead update the NDA with the 12 month results at 25°C/60%RH and 30°C/75%RH, along with updated statistical analyses. We anticipate that this update could be submitted in the second half of January 2016, and request confirmation.

3. Postmarketing Requirements/Postmarketing Commitments – 5 minutes

   As this NDA triggers PREA, pediatric studies will be required as PREA PMRs. These PMRs will reflect studies outlined in your Agreed iPSP.

4. Major labeling issues – 20 minutes

5. Review Plans – 5 minutes

   Labeling review and negotiations

6. Wrap-up and Action Items – 5 minutes

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/s/

JEFFREY S MURRAY
11/30/2015