

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203093Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

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

NDA/BLA # 203093
Product Name: VITEKTA® (elvitegravir)

PMR/PMC Description: Evaluate the pediatric pharmacokinetics (PK), safety, and antiviral activity of once daily elvitegravir combined with a background regimen including a protease inhibitor coadministered with ritonavir in HIV-1 treatment-experienced pediatric subjects from 4 weeks to less than 18 years of age. Initial evaluation of elvitegravir exposure (when combined with a protease inhibitor and ritonavir) must be performed to allow dose selection to be agreed upon with the FDA. Evaluation of longer term treatment with elvitegravir, plus background regimen including protease inhibitor and ritonavir, must assess treatment response on the basis of HIV-1 RNA virologic response and conduct safety monitoring over at least 24 weeks of dosing.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>submitted</u>
	Study/Trial Completion:	<u>4/30/2017</u>
	Final Report Submission:	<u>1/15/2018</u>
	Other:	<u>MM/DD/YYYY</u>

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

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

Adult trials are completed and drug is ready to approve; approval in adults will trigger PREA pediatric study requirements.

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

To identify appropriate dose(s) in pediatric patients and evaluate safety and antiviral activity of the agreed upon dose(s) over at least 24 weeks of dosing. Efficacy in the pediatric age groups will be based on matching the drug exposure found to be safe and effective in adults. Supporting safety data and HIV-1 RNA measurements will also be required.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

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

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

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

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

Required pharmacokinetic and safety studies in pediatric patients 4 weeks to less than 18 yrs of age.

Required

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

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

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

- Other
-

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

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

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

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

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

PMR/PMC Development Coordinator:

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

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/s/

MYUNG JOO P HONG
09/12/2014

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

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

Memorandum

Date: September 11, 2014

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

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

Subject: NDA 203093
VITEKTA (elvitegravir) tablets, for oral use

As requested in the Division of Antiviral Products' (DAVP) consult dated August 29, 2014, the Office of Prescription Drug Promotion (OPDP) has reviewed the VITEKTA prescribing information, patient labeling, and carton and container labeling.

OPDP's comments on the prescribing information are provided below in the proposed substantially complete version of the labeling received via email from DAVP on September 4, 2014.

OPDP reviewed the draft carton and container labeling submitted to the EDR on May 13, 2014, and has no comments at this time.

The Division of Medical Policy Programs and OPDP provided a single, consolidated review of the patient labeling on September 9, 2014.

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

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/s/

JESSICA M FOX
09/11/2014

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: September 9, 2014

To: Debra Birnkrant, MD
Director
Division of Antiviral Products (DAVP)

Through: Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Nathan Caulk, MS, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Jessica Fox, PharmD, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

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

Drug Name (established name): VITEKTA (elvitegravir)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 203-093

Applicant: Gilead Sciences, Inc.

1 INTRODUCTION

On April 4, 2014, Gilead Sciences, Inc. submitted for the Agency's review an original New Drug Application (NDA) 203-093 for VITEKTA (elvitegravir) tablets in response to a Complete Response (CR) letter issued on April 26, 2013. This Class 2 resubmission includes revised labeling and a response to the facility inspection deficiencies. The proposed indication for VITEKTA (elvitegravir) tablets is coadministration with a protease inhibitor/ritonavir and with other antiretroviral agents for the treatment of HIV-1 infection in antiretroviral treatment-experienced adults. The active ingredient, elvitegravir, was approved as a component of the fixed-dose combination tablet STRIBILD (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate) on August 27, 2012 under NDA 203-100.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antiviral Products (DAVP) on April 17, 2014, and August 29, 2014, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for VITEKTA (elvitegravir) tablets.

2 MATERIAL REVIEWED

- Draft VITEKTA (elvitegravir) tablets PPI received on April 4, 2014, and received by DMPP on April 17, 2014.
- Draft VITEKTA (elvitegravir) tablets PPI received on April 4, 2014, and received by OPDP on August 29, 2014.
- Draft VITEKTA (elvitegravir) tablets Prescribing Information (PI) received on April 4, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on August 28, 2014.
- Draft VITEKTA (elvitegravir) tablets Prescribing Information (PI) received on April 4, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on September 4, 2014.
- STRIBILD (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate) comparator labeling dated October 23, 2013.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more

accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

NATHAN P CAULK
09/09/2014

JESSICA M FOX
09/09/2014

BARBARA A FULLER
09/09/2014

LABEL AND LABELING REVIEW

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

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

Date of This Review: July 14, 2014
Requesting Office or Division: Division of Antiviral Products (DAVP)
Application Type and Number: NDA 203093
Product Name and Strength: Vitekta (elvitegravir) Tablets, 85 mg and 150 mg
Product Type: Single Ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Gilead Sciences, Inc.
Submission Date: May 13, 2014
OSE RCM #: 2014-798
DMEPA Primary Reviewer: Mónica Calderón, PharmD, BCPS
DMEPA Associate Director: Irene Chan, PharmD, BCPS

1 REASON FOR REVIEW

Gilead Sciences re-submitted this application, NDA 203093, for the treatment of HIV-1 infection in antiretroviral treatment-experienced adults to be coadministered with a protease inhibitor/ritonavir and with other antiretroviral agents. Gilead previously received a Complete Response under their original submission. Thus, the Division of Antiviral Products (DAVP) requested DMEPA evaluate the Applicant's proposed container labels and full prescribing information (FPI) for areas of vulnerability that could lead to medication errors. The Applicant also submitted carton labeling and container labels for the Gilead Access Program with this re-submission.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B (N/A)
Previous DMEPA Reviews	C
Human Factors Study	D (N/A)
ISMP Newsletters	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant is proposing tablets available in two strengths, 85 mg and 150 mg. The tablets will be packaged in 30-count bottles, which are supported by the dosage and administration of this product. Our review determined that the Applicant implemented all of DMEPA's previous recommendations and adequately addressed our concerns. Additionally, the changes do not appear to introduce any new risks.

This re-submission also contained carton labeling and container labels for the Gilead Access Program products which were not previously reviewed in the original submission. Our review of the carton labeling and container labels determined that the labels and labeling (b) (4)

4 CONCLUSION & RECOMMENDATIONS

Review of the revised labels and labeling show the Applicant has implemented all of DMEPA's recommendations and adequately addressed our concerns. We also did not identify any concerning areas with the Gilead Access labels and labeling. Therefore, we have no further recommendations.

If you have further questions or need clarifications, please contact Danyal Chaudhry, project manager, at 301-796-3813.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Vitekta that Gilead Sciences, Inc. submitted on April 4, 2014.

Table 2. Relevant Product Information for Vitekta	
Active Ingredient	elvitegravir
Indication	Treatment of HIV-1 infection in antiretroviral treatment-experienced adults to be coadministered with a protease inhibitor/ritonavir and with other antiretroviral agents.
Route of Administration	Oral
Dosage Form	Tablets
Strength	85 mg and 150 mg
Dose and Frequency	85 mg or 150 mg once daily
How Supplied	30-count bottles
Storage	Store at room temperature below 30 °C (86 °F).
Container Closure	Child-resistant closure

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L:drive on May 29, 2014 using the terms, Vitakta to identify reviews previously performed by DMEPA.

C.2 Results

DMEPA last reviewed proposed labels and labeling by the Applicant for their original submission of NDA 203094 (OSE Review #2012-2019) dated March 1, 2013. We made recommendations to the labels which have been implemented.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with postmarket medication error data, we reviewed the following Vitakta labels and labeling submitted by Gilead Sciences, Inc. on April 4, 2014 and May 13, 2014.

- Container label (May 13, 2014)
- Carton labeling (May 13, 2014)
- Full prescribing information (April 3, 2014)

G.2 Label and Labeling Images

Container Labels submitted May 13, 2014



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

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/s/

MONICA M CALDERON
07/14/2014

IRENE Z CHAN
07/14/2014

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

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

Memorandum

Date: April 15, 2013

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

From: Jessica Fox, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 203093
VITEKTA (elvitegravir) tablets, for oral use

DAVP's consult dated July 3, 2012, requested that OPDP review the proposed substantially complete versions of the VITEKTA prescribing information and patient information.

OPDP reviewed the proposed PI, sent via email by DAVP on April 1, 2013, and PPI, sent via email by the Division of Medical Policy Programs on April 12, 2013, and has the comments attached below.

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

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/s/

JESSICA M FOX
04/15/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: April 11, 2013

To: Debra Birnkrant, MD
Director
Division of Antiviral Products (DAVP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Nathan Caulk, MS, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

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

Drug Name (established name): VITEKTA (elvitegravir)

Dosage Form and Route: Tablets, for oral use

Application Type/Number: NDA 203-093

Applicant: Gilead Sciences, Inc.

1 INTRODUCTION

On June 27, 2012, Gilead Science, Inc. submitted for the Agency's review an Original New Drug Application (NDA) 203-093 for VITEKTA (elvitegravir) tablets. VITEKTA (elvitegravir) is a HIV-1 integrase strand transfer inhibitor. The Applicants proposed indication: VITEKTA coadministered with a protease inhibitor/ritonavir and with other antiretroviral agents, for the treatment of HIV-1 infection in antiretroviral treatment-experienced adults. The active ingredient, elvitegravir, was approved as a component of the fixed-dose combination tablet STRIBILD (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate) on August 27, 2012 under NDA 203-100. On July 3, 2012, the Division of Antiviral Products (DAVP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for VITEKTA (elvitegravir) tablets.

This review is written in response to a request by DAVP for DMPP to review the Applicant's proposed Patient Package Insert (PPI) for VITEKTA (elvitegravir) tablets.

2 MATERIAL REVIEWED

- Draft VITEKA (elvitegravir) tablets, Patient Package Insert (PPI) received on June 27, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on April 1, 2013.
- Draft VITEKTA (elvitegravir) tablets, Prescribing Information (PI) received on June 27, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on April 1, 2013.
- Pending approval TYBOST (cobicistat) tablets (NDA 203-094) comparator labeling.
- STRIBILD (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate) tablets (NDA 203-100) approved PI and PPI dated August 27, 2012.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

NATHAN P CAULK
04/11/2013

BARBARA A FULLER
04/11/2013

LASHAWN M GRIFFITHS
04/12/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: March 1, 2013

Reviewer: Morgan Walker, Pharm.D., MBA
Division of Medication Error Prevention and Analysis

Team Leader: Jamie Wilkins Parker, Pharm.D.
Division of Medication Error Prevention and Analysis

Deputy Director: Kellie Taylor, Pharm.D., MPH
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Vitekta (Elvitegravir) Tablets, 85 mg and 150 mg

Application Type/Number: NDA 203093

Applicant/sponsor: Gilead Sciences

OSE RCM #: 2012-2019

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed container labels and insert labeling for Vitekta (Elvitegravir) Tablets, 85 mg and 150 mg (NDA 203093) for areas of vulnerability that could lead to medication errors. The Applicant also submitted Vitekta carton labeling and container labels for the Gilead Access Program with this submission.

1.1 PRODUCT INFORMATION

The following product information is provided in the June 27, 2012 submission.

- Active Ingredient: Vitekta
- Established Name: Elvitegravir
- Indication of Use: With [REDACTED] ^{(b) (4)} and with other antiretroviral agents, is indicated for the treatment of HIV-1 infection in antiretroviral treatment-experienced adults. [REDACTED] ^{(b) (4)}
- Route of Administration: Oral
- Dosage Form: Tablets
- Strength: 85 mg and 150 mg
- Dose: 1 tablet once daily
- How Supplied: 30-count bottles
- Storage: This product should be stored at a controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (57°F and 86°F, respectively)

2 METHODS AND MATERIALS REVIEWED

DMEPA reviewed the Vitekta container labels and package insert labeling submitted by the Applicant. It should be noted that the Applicant also submitted carton labeling and container labels for the Gilead Access Program. However, these products will not be marketed in the United States. Therefore, DMEPA did not review the labels and labeling for the Gilead Access Program.

2.1 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

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

- Container Labels submitted June 27, 2012 (Appendix A)
- Insert Labeling submitted June 27, 2012

2.2 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously completed a proprietary name review for Vitekta in OSE Review # 2012-762 for IND 072177 and 2012-2226 for NDA 203093. The name was found acceptable.

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our risk assessment of the Vitekta container labels and insert labeling.

3.1 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

A review of the insert labeling did not identify any vulnerability that may contribute to medication errors. However, a review of the container labels identified the following vulnerability that may lead to medication errors:

- Revise the color of the shaded box which highlights the strength statement to a distinct color for each strength of the product to provide adequate differentiation between the two strengths.

4 CONCLUSIONS

DMEPA concludes that the proposed container labels can be improved to increase the differentiation between the two strengths, 85 mg and 150 mg to promote the safe use of the product.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Comments to the Applicant

- Container Labels
 - Revise the color of the shaded box behind the strengths, 85 mg and 150 mg, to two different colors to provide adequate strength differentiation between the two strengths.

If you have further questions or need clarifications, please contact Danyal Chaudhry, project manager, at 301-796-3813.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Appendix B: Container Labels



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/s/

MORGAN A WALKER
03/01/2013

JAMIE C WILKINS PARKER
03/01/2013

KELLIE A TAYLOR
03/01/2013

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: February 26, 2013

TO: Myung-Joo Patricia Hong, M.S., Regulatory Health Project Manager
Russ Fleischer, PA-C, MPH, Clinical Reviewer
Division of Antiviral Drug Products

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

THROUGH: Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

SUBJECT: Evaluation of Clinical Inspections

NDA: 203-093

APPLICANT: Gilead Sciences, Inc.

DRUG: Vitekta[®] (elvitegravir)

NME: No

THERAPEUTIC CLASSIFICATION: Standard review
INDICATION: Combination with antiretroviral agents for the treatment of HIV-1
infection in antiretroviral (ARV) treatment-experienced adults
CONSULTATION REQUEST DATE: August 10, 2012
DIVISION ACTION GOAL DATE: April 26, 2013

INSPECTION SUMMARY GOAL DATE: March 25, 2013

PDUFA DATE: April 26, 2013

I. BACKGROUND:

Gilead Sciences, Inc. submitted this application for the use of daily administration of elvitegravir (EVG) and Raltegravir (RAL) and matching placebo by treatment arm in the treatment-experienced HIV-1 infected adults. One clinical trial was submitted in support of the application: Study GS-US-183-0145.

Investigational Drug

Gilead has developed GS-9137 (elvitegravir), a first-in-class pharmacoenhancer agent to be used with specific protease inhibitor drugs for the treatment of HIV-1 infection. GS-9137 is devoid of anti-HIV activity, may have less adverse biochemical effects such as lipid accumulation relative to ritonavir, and can be coformulated as a tablet with other agents that require boosting. GS-9137 is a structural analogue of ritonavir (RTV), and has been shown to be an irreversible inhibitor of CYP3A enzymes with greater specificity than RTV. GS-9137 is being developed as a pharmacoenhancer (booster) to increase the systemic levels of coadministered agents metabolized by CYP3A enzymes, (b) (4)

Although elvitegravir is not an NME, it is currently being reviewed as part of an application for a fixed-dose combination tablet of EVG/FTC/TDF/GS-9350 which resulted in a sustained virologic response (SVR); i.e., a substantial decrease in the presence of HIV RNA and an increase in CD4 counts. The applicant is seeking to market elvitegravir as a new stand-alone agent. Safety and efficacy in support of the application are based primarily on 48-week data from GS-US 1836-0114, a phase 3 trial comparing ritonavir boosted elvitegravir versus raltegravir in treatment-experienced HIV-1 infected subjects.

Protocol GS-US-183-0145

Protocol GS-US-183-0145 entitled, “A Multicenter, Randomized, Double-blind, Double-Dummy, Phase 3 Study of the Safety and Efficacy of Ritonavir-Boosted Elvitegravir (EVG/r) versus Raltegravir (RAL) Each Administered with Background Regimen in HIV-1 Infected, Antiretroviral Treatment-Experienced Adults” was a double-blind, double-dummy, multicenter, randomized, active-controlled study to assess the safety and efficacy of a regimen containing ritonavir-boosted elvitegravir versus raltegravir, each administered with a background regimen (BR) containing a fully active ritonavir-boosted protease inhibitor and a second agent in HIV-1 infected, antiretroviral and treatment-experienced adults.

The objective of this study was to assess non-inferiority of a regimen containing ritonavir-boosted elvitegravir versus raltegravir, each administered with a background regimen (BR) in HIV-1 infected, antiretroviral treatment-experienced adult subjects as determined by the proportion of subjects achieving and maintaining confirmed HIV-1 RNA < 50 copies/mL through week 48.

The secondary objective of this study was to evaluate the efficacy, safety, and tolerability of two treatment arms through 48 weeks of treatment.

Subjects were on a stable antiretroviral regimen for at least 30 days prior to the screening visit. Prior to randomization, the components of BR were selected by the investigator based on each subjects’ antiretroviral drug history and results of the screening viral resistance profile. Eligible subjects were randomized in a 1:1 ratio to one of the following two treatment arms:

Treatment Arm 1: Ritonavir-boosted elvitegravir 150 mg QD (ritonavir-boosted elvitegravir 85 mg QD for subjects taking atazanavir/r or lopinavir/r as part of their BR) + raltegravir placebo BID + BR (N= 350).

Treatment Arm 2: Raltegravir 400mg BID +elvitegravir placebo QD +BR (n=350).

GS-US-183-0145: Daily Administration of Elvitegravir and Raltegravir and Matching Placebo by Treatment Group

Randomization	Ritonavir-Boosted PI	
	ATV/r or LPV/r	DRV/r, FPV/r, TPV/r
Treatment Group 1 EVG/r + BR	EVG 85 mg (pentagon) once daily RAL 400 mg placebo (oval) twice daily	EVG 150 mg (triangle) once daily RAL 400 mg placebo (oval) twice daily
Treatment Group 2 RAL + BR	EVG 85 mg placebo (pentagon) once daily RAL 400 mg (oval) twice daily	EVG 150 mg placebo (triangle) once daily RAL 400 mg (oval) twice daily

ATV, atazanavir; DRV, darunavir; FPV, fosamprenavir; LPV, lopinavir; /r, boosted with ritonavir; TPV, tipranavir

Subjects received darunavir/r (DRV/r), fosamprenavir/r (FPV/r), or tipranavir/r (TPV/r) as part of their BR received EVG 150 mg if randomized to Treatment Group 1. Due to known PK interactions, subjects received ATV/r or lopinavir (LPV)/r as part of their BR received EVG 85 mg if randomized to Treatment Group 1.

The review division requested inspection of three domestic clinical investigators who enrolled in the pivotal protocol Study GS-US-183-0145. The consult to OSI states, “The sites were selected on the basis of the relatively large enrollment of subjects, high treatment responders, and significant primary efficacy results pertinent to decision-making”.

II. RESULTS (by protocol/site):

Name of CI, location, and site #	Protocol and # of subjects	Inspection Dates	Final Classification
Joseph Gathe, Jr., M.D. 4900 Fannin Street Houston, TX 77478 Site #0031	Protocol GS-US-183-0145 Number of Subjects: 34	October 24 to November 5, 2012	Pending (Preliminary classification NAI)
Anthony LaMarca, M.D. Therafirst Medical Centers 4011 North Federal Highway Fort Lauderdale, FL 33308 Site # 0566	Protocol GS-US-183-0145 Number of Subjects: 43	October 9 to 11, 2012	NAI
Thomas Jefferson, M.D. Health for life Clinic, LLC 1100 North University Avenue, Suite 260 Little Rock, AR 72207 Site #1965	Protocol GS-US-183-0145 Number of Subjects 13	October 22 to 26, 2012	Pending (Preliminary classification NAI)

Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations for regulations. Data unreliable.

Pending = Preliminary classification based on e-mail communication from the field; the EIR has not been received from the field and complete review of EIR is pending.

1. **Joseph C. Gathe Jr, M.D.**
Houston TX 77004

a. What Was Inspected: At this site, 50 subjects were screened, 16 subjects were reported as screen failures, 34 subjects were randomized, and 20 were prematurely terminated for not meeting inclusion criteria; 14 subjects were actively enrolled in the study. Review of the Informed Consent Documents, for all subjects records reviewed, verified that subjects signed informed consent prior to enrollment.

The medical records/source documents for 25 subjects were reviewed in depth, including drug accountability records, vital signs, IRB files, laboratory results, inclusion/exclusion criteria, and use of concomitant medications. Source documents for all 25 subjects were compared to case report forms and data listings, to include primary efficacy endpoint and adverse events.

b. General observations/commentary: At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Gathe. The medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.

c. Assessment of Data Integrity: The data in support of the clinical efficacy and safety at Dr. Gathe’s site are considered reliable and appear acceptable in support of the application.

2. **Anthony LaMarca, M. D.**
Ft Lauderdale, FL 33308

a. What Was Inspected: At this site, a total of 57 were screened and 14 subjects were reported as screen failures. Forty three subjects were randomized, seven subjects were lost to follow-up, and nine subjects withdrew (the reason(s) were documented). Two subjects withdrew from the 24 subjects who remained on the open-label portion of the study and one subject died. Twenty seven of the 57 subjects’ files were reviewed. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed consent forms prior to enrollment.

The medical records/source data for all 27 subjects enrolled were reviewed which included: three screen failures, three lost to follow-up, nine subjects who withdrew from the study, one subject who died and 11 subjects who remained on the study. The review focused on drug accountability records, vital signs, laboratory results, IRB records, prior and current medications, and inclusion/exclusion criteria. There was no evidence of under-reporting of adverse events. Source documents were compared to CRFs and data listings for primary efficacy endpoints and adverse events listing.

b. General Observations/Commentary: At the conclusion of the inspection, no Form FDA 483 was issued to Dr. LaMarca. The medical records reviewed were found to be in order, organized, and the data verifiable. There were no known limitations to the inspection.

c. Assessment of Data Integrity: The data generated at Dr. LaMarca’s site in support of clinical efficacy and safety are considered acceptable and may be used in support of the pending application.

3. **Thomas Jefferson, M.D.**
Little Rock, AR 72207

a. What Was Inspected: At this site, a total 41 subjects were screened, 28 subjects were reported as screen failures, 13 subjects were randomized into the study, five subjects completed the study and rolled over to the open-label. Eight subjects discontinued early and the reason(s) documented. Review of the Informed Consent Documents, for all subjects records reviewed, verified that all subjects signed consent forms prior to enrollment.

The medical records/source documents for all subjects were partially reviewed for primary/secondary endpoints and informed consent. The medical records/source documents for 13 subjects were reviewed in depth, including drug accountability

records, vital signs, IRB files, laboratory test results, inclusion/exclusion criteria, and use of concomitant medications. Source documents for subjects were compared to case report forms and data listings for the primary efficacy endpoints and adverse events

b. General Observations/Commentary: At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Jefferson. However, our field investigator found that one subject received prohibited medication by an outside physician and another subject was under dosed for about one month due to an error by the study coordinator. The medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.

c. Assessment of Data Integrity: The data submitted in support of the clinical efficacy and safety at Dr. Jefferson's site are considered reliable and appear acceptable in support of the pending application.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Three clinical investigator sites were inspected in support of this application. The inspections of Drs. Gathe, LaMarca, and Jefferson revealed no regulatory violations, and the classifications for these inspections are noted above. The classification for the inspection of Dr. LaMarca is No Action Indicated (NAI). The final classification for Dr. Gathe's and Jefferson's sites will be determined upon review of the establishment inspection reports (EIR). An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR. While minor observations were identified during the inspection of Dr. Jefferson, the findings are not likely to critically impact primary efficacy and safety analyses; therefore, OSI does not consider the effect of the violations on overall data integrity to be significant. Overall, the data submitted from these three sites are considered acceptable in support of the pending application.

{See appended electronic signature page}

Antoine El-Hage, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
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CONCURRENCE:

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Acting Team Leader
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{See appended electronic signature page}

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Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

/s/

ANTOINE N EL HAGE
02/26/2013

SUSAN LEIBENHAUT
02/26/2013

SUSAN D THOMPSON
02/26/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 203093 Original Submission	NDA Supplement #: BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Vitakta Established/Proper Name: Elvitegravir Dosage Form: Tablet Strengths: 85 and 150 mg		
Applicant: Gilead Sciences, Inc. Agent for Applicant (if applicable):		
Date of Application: June 27, 2012 Date of Receipt: June 27, 2012 Date clock started after UN:		
PDUFA Goal Date: April 27, 2013		Action Goal Date (if different): April 26, 2013
Filing Date: August 26, 2012		Date of Filing Meeting: August 13, 2012
Chemical Classification: (1, 2, 3 etc.) (original NDAs only): Type 5		
Proposed indication(s)/Proposed change(s): In combination with a ritonavir boosted protease inhibitor and other antiretroviral (ARV) agents for the treatment of HIV-1 infection in ARV treatment-experienced adults		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 72,177, MF (b) (4), MF (b) (4), MF (b) (4), MF (b) (4), NDA 203100				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	✓			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	✓			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	✓			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		✓		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	✓			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>		<p>✓</p>																		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>		✓		
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDA/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: 5 years/3 years</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	✓			If the Stribild (NDA 203100) is approved, 3 years is requested. If not approved, 5 years was requested.
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA only</i>)?</p>		✓		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	✓			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	✓			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDA/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	✓			

1

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

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)	YES	NO	NA	Comment
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			✓	
<ul style="list-style-type: none"> If yes, were all of them submitted on time? 				
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?			✓	
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?			✓	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	✓			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	✓			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	✓			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	✓			

<p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	✓			
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	✓			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			✓	Not needed since this is an electronic submission.
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>		✓		

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	✓			PeRC review meeting scheduled on February 27, 2013
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>		✓		
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>	✓			<p>1. Partial waiver request for newborn infants (birth to <4 weeks).</p> <p>2. Deferral request for subjects 4 weeks to < 18 years of age ((b) (4))</p> <p>3. Partial pediatric study (Study GS-US-183-0152, 12 to < 18 yrs of age) was completed and final study report was submitted.</p>
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</p> <p><i>If no, request in 74-day letter</i></p>	✓			
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i></p>		✓		
<p><u>Proprietary Name</u></p> <p>Is a proposed proprietary name submitted?</p>				Approved by DMEPA under IND

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				72177: "Vitekta"
REMS	YES	NO	NA	Comment
Is a REMS submitted?		✓		
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	✓			
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	✓			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted, what is the status of the request?				
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	✓			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	✓			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	✓			
OTC Labeling	<input type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL)			

4

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

	<input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): March 12, 2010 <i>If yes, distribute minutes before filing meeting</i>				One EOP 2 meeting for all three INDs: IND 72,177 - EVG IND 101,283 – COBI IND 103,093 – FDC
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>				Pre-NDA was scheduled on 3/5/12; however, Gilead cancelled after receiving FDA's preliminary comments (3/1/12)
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 13, 2012

NDA #: 203093

PROPRIETARY NAME: Vitekta

ESTABLISHED/PROPER NAME: Elvitegravir

DOSAGE FORM/STRENGTH: 85 and 150 mg Tablets

APPLICANT: Gilead Sciences, Inc.

PROPOSED INDICATION: Treatment of HIV-1 infection in ARV treatment-experienced adults.

BACKGROUND:

Gilead Sciences, Inc. submitted an NDA application for Elvitegravir tablets. Elvitegravir, a human immunodeficiency virus type (HIV-1) integrase strand transfer inhibitor, co-administered with a ritonavir-boosted protease inhibitor (PI/r) and other antiretroviral (ARV) agents, is indicated for the treatment of HIV-1 infection in ARV treatment-experienced adults.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Myung-Joo P. Hong, M.S.	Y
	CPMS/TL:	Karen Winestock	Y
Cross-Discipline Team Leader (CDTL)	Linda Lewis, M.D.		Y
Clinical	Reviewer:	Russ Fleischer, PA-C, MPH	Y
	TL:	Linda Lewis, M.D.	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		

	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	Sung Rhee, Ph.D.	N
	TL:	Jules O'Rear, Ph.D.	Y
Clinical Pharmacology	Reviewer:	Leslie Chinn, Ph.D. Dhananjay Maranthe, Ph.D. (Pharmacometrics)	Y Y
	TL:	Shirley Seo, Ph.D.	Y
Biostatistics	Reviewer:	Lei Nie, Ph.D.	Y
	TL:	Greg Soon, Ph.D.	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Pritam Verma, Ph.D.	N
	TL:	Hanan Ghantous, DABT, Ph.D.	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Milton Sloan, Ph.D. (DS) Celia Cruz, Ph.D. (DP) Kareen Riviere, Ph.D. (Biopharm)	Y Y Y
	TL:	Stephen Miller, Ph.D. Angelica Dorante, Ph.D.	N N
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Morgan Walker	Y
	TL:	Jamie Wilkins Parker	N
OSE/DRISK (REMS)	Reviewer:		

	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:	Antoine El Hage	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	OMPT – Nathan Caulk		Y
	Barbara Fuller		Y
	OPDP – Jessica Fox		N
	Kemi Asante		N
Other attendees	Kendall Marcus, Peter Miele, Kim Struble, Paula Gish, Darrell Jenkins, James Trinidad		Y

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
CLINICAL	
<p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES – 3 domestic sites selected (Florida, Arkansas, and Texas) <input type="checkbox"/> NO

<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter

<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments: Inspection request is pending.</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>REGULATORY PROJECT MANAGEMENT</p>	
<p>Signatory Authority: Debra Birnkrant, M.D.</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): November 28, 2012</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
<p>REGULATORY CONCLUSIONS/DEFICIENCIES</p>	
<p><input type="checkbox"/></p>	<p>The application is unsuitable for filing. Explain why:</p>
<p><input checked="" type="checkbox"/></p>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
<p>ACTIONS ITEMS</p>	
<p><input checked="" type="checkbox"/></p>	<p>Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).</p>
<p><input type="checkbox"/></p>	<p>If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).</p>

<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

MYUNG JOO P HONG
08/15/2012

KAREN D WINESTOCK
08/17/2012

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

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: 203-093/OS

Application Type: New NDA

Name of Drug: Vitekta (Elvitegravir), 85 and 150 mg Tablets

Applicant: Gilead Sciences, Inc.

Submission Date: June 27, 2012

Receipt Date: June 27, 2012

1.0 Regulatory History and Applicant's Main Proposals

Gilead Sciences, Inc. (Gilead) submitted a New Drug Application (NDA) for elvitegravir (EVG) 85 mg and 150 mg tablets for use once daily as part of an antiretroviral (ARV) regimen that includes a ritonavir-boosted protease inhibitor (PI/r) and other ARV agents for the treatment of HIV-1 infection in ARV treatment-experienced adults.

Elvitegravir is a new chemical entity that belongs to the novel class of HIV-1 integrase strand transfer inhibitors (INSTIs) that prevent integration of HIV-1 genetic material into the host-cell genome. Additionally, EVG is a component in the 4-drug fixed-dose combination tablet (the QUAD single-tablet regimen [STR]) which is comprised of EVG, a pharmacokinetic enhancer cobicistat (COBI), and the current standard-of-care dual NRTI/NtRTI backbone FTC/TDF (Truvada® [TVD]).

2.0 Review of the Prescribing Information (PI)

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

3.0 Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI. However, the following some corrections outside the scope of the SRPI will be conveyed to the sponsor.

Under Highlights

1. The route of administration should follow after the dosage form.
[TRADENAME] (elvitegravir) tablets, **for oral use**

Selected Requirements of Prescribing Information (SRPI)

2. The following information should be deleted from the Use in Specific Populations section:
 - a. Pregnancy Registry available
 - b. Pediatrics: Not recommended for patients less than 18 years of age. (8.4)

Under the Full Prescribing Information

3. Several sub-subsection headings are bolded under subsection 12.3 and 12.4. The sponsor will be asked to remove the bold.

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.
- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).
- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.
- YES** 4. White space must be present before each major heading in HL.
- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).
- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required

Selected Requirements of Prescribing Information (SRPI)

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

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

HIGHLIGHTS DETAILS

Highlights Heading

YES

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

Highlights Limitation Statement

YES

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Product Title

YES

10. Product title in HL must be **bolded**.

Comment: Route of administration “For oral use” needs to be added at the end of product title.

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Boxed Warning

N/A

12. All text must be **bolded**.

N/A

Selected Requirements of Prescribing Information (SRPI)

13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Dosage Forms and Strengths

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment: *Tablular form was used for two dosage strengths (85 and 150 mg).*

Selected Requirements of Prescribing Information (SRPI)

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment: *No contraindication listed.*

N/A

24. Each contraindication is bulleted when there is more than one contraindication.

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):
If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

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

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment: *“See 17 for PATIENT COUNSELING INFORMATION and FDA- Approved Patient Labeling” was selected.*

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.
-

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.
- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.
- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Selected Requirements of Prescribing Information (SRPI)

- YES** 32. All section headings must be **bolded** and in UPPER CASE.
- YES** 33. All subsection headings must be indented, not bolded, and in title case.
- YES** 34. When a section or subsection is omitted, the numbering does not change.
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
- YES** 37. All section and subsection headings and numbers must be **bolded**.
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action

Selected Requirements of Prescribing Information (SRPI)

12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.
- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].
- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.
- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).
- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Contraindications

- YES** 45. If no Contraindications are known, this section must state “None”.

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

Selected Requirements of Prescribing Information (SRPI)

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

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment: “See FDA-approved patient labeling (Patient Information)” was listed.

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

/s/

MYUNG JOO P HONG
08/03/2012

KAREN D WINESTOCK
08/07/2012