

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**210251Orig1s000**

**OTHER REVIEW(S)**

## PMR/PMC DEVELOPMENT TEMPLATE

For 506B Reportable<sup>1</sup> PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

**Note:** Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.<sup>1</sup>

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### SECTION A: Administrative Information

**NDA #** 210251  
**PMR/PMC Set (####-#)** 3322-1  
**Product Name:** BIKTARVY (bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide tablets 25 mg) (B/F/TAF)  
**Applicant Name:** Gilead Sciences, Inc.  
**ODE/Division:** OAP/DAVP

### SECTION B: PMR/PMC Information

#### 1. PMR/PMC Description

Conduct a study in patients 2 years to <18 years old who are HIV-1 infected, virologically suppressed (HIV-1 RNA <50 copies/mL) and on a stable antiretroviral regimen at the time of enrollment, to assess the pharmacokinetics, safety and tolerability, and antiviral activity of bictegravir/emtricitabine/tenofovir alafenamide as part of a fixed dose combination (FDC) product. Study participants must be monitored for a minimum of 24 weeks to assess safety and durability of antiviral response.

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#### 2. PMR/PMC Schedule Milestones<sup>2, 3</sup>

Final Protocol Submission: 08/2018  
Study/Trial Completion: 12/2020  
Final Report Submission: 05/2021

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<sup>1</sup> 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

<sup>2</sup> Final protocol, study/trial completion, and final report submissions are required milestones. Draft protocol submissions and interim milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

<sup>3</sup> Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

## **SECTION C: PMR/PMC Rationale**

### **1. Describe the particular review issue and the goal of the study<sup>4</sup> or clinical trial<sup>5</sup> in the text box below.**

- Adult trials are completed and ready for approval. The goal of the deferred study is to determine the pharmacokinetic (PK) profile of B/F/TAF component drugs in pediatric patients from 2 years of age to <18 years of age, to determine appropriate dose(s) that results in exposure similar to that found to be safe and effective in adult patients, and provide safety information in this pediatric age group. At least some of the safety data must be derived from dosing as the B/F/TAF fixed dose combination (duration and number of subjects on B/F/TAF to be agreed upon with the Agency).

### **2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)**

- Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- PREA PMR: Meets PREA postmarketing pediatric study *requirements* [\[Skip to Q.5\]](#)
- FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug’s safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)
- PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug’s efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

### **3. For FDAAA PMRs and 506B PMCs only**

**The study or trial can be conducted post-approval because:** [\[Select all that apply\]](#)

- Longer-term data needed to further characterize the safety/efficacy of the drug
- Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized

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<sup>4</sup> A “study” is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

<sup>5</sup> A “clinical trial” is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.”

- Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- Study/trial is to further explore a theoretical concern that does not impact the approval determination
- Other reason (describe in text box below)

4. **For FDAAA PMRs only [for PMCs skip to Q.5]. Complete this entire section**

**a. The purpose of the study/clinical trial is to: [Select one, then go to Q.4.b ]**

- Assess a known serious risk related to the use of the drug
- Assess a signal 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

*Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.*

**b. FAERS<sup>6</sup> and Sentinel’s postmarket ARIA<sup>7</sup> system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

*[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d ]*

- A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

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<sup>6</sup> FDA Adverse Event Reporting System (FAERS)

<sup>7</sup> Active Risk Identification and Analysis (ARIA)

**Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply**

**c. FAERS data cannot be used to fully characterize the serious risk of interest because:**

*[Select all that apply then go to Q.4.d ]*

- Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- Other

**Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.**

**d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e ]***

- Cannot identify exposure to the drug(s) of interest in the database.
- Serious risk (adverse event) of concern cannot be identified in the database.
- The population(s) of interest cannot be identified in the database.
- Long-term follow-up information required to assess the serious risk are not available in the database.
- Important confounders or covariates are not available or well represented in the database.
- The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- Other

e. **If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?** *[Select either “Yes” or “No” and provide the appropriate responses.]*

**Yes, a study is sufficient** *[Explain your answer in the textbox and then go to Q.5]*

**No, a study is not sufficient** *[Select all explanations that apply then go to Q.4.f]*

- Need to minimize bias and/or confounding via randomization
- Need for placebo control
- Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- Other

f.  **Because a study is not sufficient, a clinical trial is required.** *[Go to Q.5]*

5. **For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal described in**

**Q1 *or* Q4.a above?**

*[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]*

**TYPE OF STUDY**

- Drug interaction or bioavailability studies (nonclinical only)
- Epidemiologic (observational) study related to safe drug use
- Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Immunogenicity study (nonclinical)
- Meta-analysis or pooled analysis of previous observational studies
- Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)

### TYPE OF STUDY

- Pharmacogenetic or pharmacogenomic study
- Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- Quality CMC study (e.g., manufacturing, studies on impurities)
- Quality stability study
- Registry-based observational study
- Other (describe) This open-label, single-arm study will be conducted in HIV-1 infected patients from 2 to less than 18 years of age, who are virologically suppressed (HIV-1 RNA <50 copies/mL) and on a stable antiretroviral regimen at the time of enrollment, to assess the pharmacokinetics, safety and tolerability, and antiviral activity of age-appropriate doses of B/F/TAF given in combination. \_\_\_\_\_

### TYPE OF CLINICAL TRIAL

- Combined PK/PD, safety and/or efficacy trial (*PREA\* PMRs only*)
- Dose-response clinical trial
- Dosing trial (e.g., alternative dosing schedule)
- Drug interaction or bioavailability clinical trial (clinical only)
- Immunogenicity trial (clinical)
- Meta-analysis or pooled analysis of previous clinical trials
- Pharmacogenetic or pharmacogenomic clinical trial
- Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- Safety outcomes trial (SOT)\*\*
- Thorough Q-T clinical trial
- Other (describe) \_\_\_\_\_

\* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

\*\* A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

**SECTION D: PMR/PMC Additional Information**

**1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).**

Yes

No

**2. This study or clinical trial focuses on the following special population(s) or circumstance(s):**  
*[Select all that apply]*

For *non-PREA* pediatric studies/trials only: Pediatric population

Geriatric population

Lactating/nursing mothers

Medical Countermeasures (e.g. anthrax exposure, bioterrorism)

Orphan or rare disease population

Pregnant women

Racial/ethnic population

Not applicable

**3. (Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

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## **SECTION E: PMR/PMC Development Coordinator Statements<sup>8</sup>**

**1. The PMR/PMC is clear, feasible, and appropriate<sup>9</sup> because: *[Select all that apply]***

- The study/clinical trial meets criteria for a PMR or a PMC.
- The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- The applicant has adequately justified the choice of milestone dates.
- The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

**2.  (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:**

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

**3.  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.**

Refer to DARRTS electronic signature (Deputy Director for Safety)

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<sup>8</sup> This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

<sup>9</sup> See POLICY section of CDER MAPP 6010.9.

## PMR/PMC DEVELOPMENT TEMPLATE

For 506B Reportable<sup>1</sup> PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

**Note:** Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.<sup>1</sup>

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### SECTION A: Administrative Information

**NDA #** 210251  
**PMR/PMC Set (#####-#)** 3322-2  
**Product Name:** BIKTARVY (bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide tablets 25 mg) (B/F/TAF)  
**Applicant Name:** Gilead Sciences, Inc.  
**ODE/Division:** OAP/DAVP

### SECTION B: PMR/PMC Information

#### 1. PMR/PMC Description

Conduct a study in HIV-1 infected, treatment naïve patients at least 4 weeks and weighing 4 to 12 kg to assess the pharmacokinetics, safety and tolerability, and antiviral activity of bictegravir/emtricitabine/tenofovir alafenamide. Study participants must be monitored for a minimum of 24 weeks to assess safety and durability of antiviral response.

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#### 2. PMR/PMC Schedule Milestones<sup>2, 3</sup>

Final Protocol Submission: 08/2019  
Study/Trial Completion: 02/2022  
Final Report Submission: 06/2022

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<sup>1</sup> 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

<sup>2</sup> Final protocol, study/trial completion, and final report submissions are required milestones. Draft protocol submissions and interim milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

<sup>3</sup> Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

## **SECTION C: PMR/PMC Rationale**

### **1. Describe the particular review issue and the goal of the study<sup>4</sup> or clinical trial<sup>5</sup> in the text box below.**

- Adult trials are completed and ready for approval.
- The goal of the deferred study is to determine the pharmacokinetics (PK) profile of B/F/TAF component drugs in pediatric patients at least 4 weeks and weighing 4 to 12 kg, to determine appropriate dose(s) that results in exposure similar to that found to be safe and effective in adult patients, and provide safety information in this pediatric age group. An assessment of antiviral activity will be performed to further support extrapolation of efficacy from the adult clinical trials. At least some of the safety data must be derived from dosing as the B/F/TAF fixed dose combination (duration and number of subjects on B/F/TAF to be agreed upon with the Agency).

### **2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)**

- Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- PREA PMR: Meets PREA postmarketing pediatric study *requirements* [\[Skip to Q.5\]](#)
- FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)
- PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

### **3. For FDAAA PMRs and 506B PMCs only**

**The study or trial can be conducted post-approval because:** [\[Select all that apply\]](#)

- Longer-term data needed to further characterize the safety/efficacy of the drug
- Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval

<sup>4</sup> A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

<sup>5</sup> A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

- Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- Study/trial is to further explore a theoretical concern that does not impact the approval determination
- Other reason (describe in text box below)

4. **For FDAAA PMRs only** *[for PMCs skip to Q.5]. Complete this entire section*

a. **The purpose of the study/clinical trial is to:** *[Select one, then go to Q.4.b ]*

- Assess a known serious risk related to the use of the drug
- Assess a signal 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

*Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.*

b. **FAERS<sup>6</sup> and Sentinel’s postmarket ARIA<sup>7</sup> system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

*[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d ]*

- A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

<sup>6</sup> FDA Adverse Event Reporting System (FAERS)

<sup>7</sup> Active Risk Identification and Analysis (ARIA)

**Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply**

**c. FAERS data cannot be used to fully characterize the serious risk of interest because:**

*[Select all that apply then go to Q.4.d ]*

- Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- Other

**Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.**

**d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e ]***

- Cannot identify exposure to the drug(s) of interest in the database.
- Serious risk (adverse event) of concern cannot be identified in the database.
- The population(s) of interest cannot be identified in the database.
- Long-term follow-up information required to assess the serious risk are not available in the database.
- Important confounders or covariates are not available or well represented in the database.
- The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- Other

e. **If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?** *[Select either “Yes” or “No” and provide the appropriate responses.]*

**Yes, a study is sufficient** *[Explain your answer in the textbox and then go to Q.5]*

**No, a study is not sufficient** *[Select all explanations that apply then go to Q.4.f]*

- Need to minimize bias and/or confounding via randomization
- Need for placebo control
- Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- Other

f.  **Because a study is not sufficient, a clinical trial is required.** *[Go to Q.5]*

5. **For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal described in**

**Q1 *or* Q4.a above?**

*[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]*

**TYPE OF STUDY**

- Drug interaction or bioavailability studies (nonclinical only)
- Epidemiologic (observational) study related to safe drug use
- Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Immunogenicity study (nonclinical)
- Meta-analysis or pooled analysis of previous observational studies
- Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)

### TYPE OF STUDY

- Pharmacogenetic or pharmacogenomic study
- Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- Quality CMC study (e.g., manufacturing, studies on impurities)
- Quality stability study
- Registry-based observational study
- Other (describe) This open-label, single-arm study will be conducted in HIV-infected treatment-naïve patients at least 4 weeks and weighing 4 to 12 kg to assess the pharmacokinetics, safety and tolerability, and antiviral activity of age-appropriate dose(s) of B/F/TAF given in combination.

### TYPE OF CLINICAL TRIAL

- Combined PK/PD, safety and/or efficacy trial (*PREA\* PMRs only*)
- Dose-response clinical trial
- Dosing trial (e.g., alternative dosing schedule)
- Drug interaction or bioavailability clinical trial (clinical only)
- Immunogenicity trial (clinical)
- Meta-analysis or pooled analysis of previous clinical trials
- Pharmacogenetic or pharmacogenomic clinical trial
- Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- Safety outcomes trial (SOT)\*\*
- Thorough Q-T clinical trial
- Other (describe) \_\_\_\_\_

\* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

\*\* A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

### SECTION D: PMR/PMC Additional Information

**1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).**

- Yes
- No

**2. This study or clinical trial focuses on the following special population(s) or circumstance(s):**

*[Select all that apply]*

- For non-PREA pediatric studies/trials only: Pediatric population
- Geriatric population
- Lactating/nursing mothers
- Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- Orphan or rare disease population
- Pregnant women
- Racial/ethnic population
- Not applicable

**3. (Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

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**SECTION E: PMR/PMC Development Coordinator Statements<sup>8</sup>**

**1. The PMR/PMC is clear, feasible, and appropriate<sup>9</sup> because: *[Select all that apply]***

- The study/clinical trial meets criteria for a PMR or a PMC.
- The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- The applicant has adequately justified the choice of milestone dates.
- The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

**2.  (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.

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<sup>8</sup> This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

<sup>9</sup> See POLICY section of CDER MAPP 6010.9.

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

3.  **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.**

Refer to DARRTS electronic signature (Deputy Director for Safety)

## PMR/PMC DEVELOPMENT TEMPLATE

For 506B Reportable<sup>1</sup> PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

**Note:** Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.<sup>1</sup>

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### SECTION A: Administrative Information

**NDA #** 210251  
**PMR/PMC Set (####-#)** 3322-3  
**Product Name:** BIKTARVY (bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide tablets 25 mg) (B/F/TAF)  
**Applicant Name:** Gilead Sciences, Inc.  
**ODE/Division:** OAP/DAVP

### SECTION B: PMR/PMC Information

#### 1. PMR/PMC Description

Conduct a study to evaluate the pharmacokinetics and safety of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) in neonates (birth to less than 4 weeks of age) who are HIV-1 infected or exposed and at high risk of infection to identify the appropriate dose and establish the safety of B/F/TAF.

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#### 2. PMR/PMC Schedule Milestones<sup>2, 3</sup>

Final Protocol Submission: 01/2021  
Study/Trial Completion: 02/2022  
Final Report Submission: 06/2022

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<sup>1</sup> 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

<sup>2</sup> Final protocol, study/trial completion, and final report submissions are required milestones. Draft protocol submissions and interim milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

<sup>3</sup> Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

## SECTION C: PMR/PMC Rationale

### 1. Describe the particular review issue and the goal of the study<sup>4</sup> or clinical trial<sup>5</sup> in the text box below.

- Adult trials are completed and ready for approval.
- The goal of the deferred study is to determine the pharmacokinetic (PK) profile of bicitgravir/emtricitabine/tenofovir alafenamide (B/F/TAF) in pediatric patients from birth to less than 4 weeks of age, to determine the appropriate dose(s) that results in exposure similar to that found to be safe and effective in adult patients, and provide some limited safety information in this pediatric age group.
- Neonates exposed to HIV-1 infected mothers are at risk of developing HIV-1; particularly those born to mothers who were not treated with antiretrovirals during their pregnancy.
- Antiretroviral therapy in the neonatal time should be safe and efficacious and not cause untoward effects on the development of organ structures. B/F/TAF has a safety profile and appropriate nonclinical studies to support evaluation in the neonatal population.
- Combination antiretroviral therapy is recommended for neonates with HIV-1 infection or those at high risk of HIV-1 infection.
- Currently, the availability of rapid and reliable HIV-1 testing and the ability to start more than one antiretroviral very early or immediately after birth allows for enrollment of neonates into trials, further benefiting the HIV-1 exposed neonate by decreasing the potential for HIV-1 infection, or for the infected neonate, may potentially produce a prolonged remission or lead to a better outcome with HIV-1.
- Establishing adequate PK of antiretroviral drug in neonates with combination antiretroviral therapy to prevent or treat HIV-1 infection is needed. B/F/TAF could provide another highly active combination therapy option for neonates who are infected or are at high risk of HIV-1 infection.

### 2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval.

(Select one explanation below.)

- Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- PREA PMR: Meets PREA postmarketing pediatric study *requirements* [\[Skip to Q.5\]](#)
- FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)
- PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

<sup>4</sup> A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

<sup>5</sup> A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

**3. For FDAAA PMRs and 506B PMCs only**

**The study or trial can be conducted post-approval because:** *[Select all that apply]*

- Longer-term data needed to further characterize the safety/efficacy of the drug
- Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- Study/trial is to further explore a theoretical concern that does not impact the approval determination
- Other reason (describe in text box below)

**4. For FDAAA PMRs only *[for PMCs skip to Q.5]. Complete this entire section***

**a. The purpose of the study/clinical trial is to:** *[Select one, then go to Q.4.b ]*

- Assess a known serious risk related to the use of the drug
- Assess a signal 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

*Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.*

**b. FAERS<sup>6</sup> and Sentinel’s postmarket ARIA<sup>7</sup> system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

*[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d ]*

- A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

*Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply*

**c. FAERS data cannot be used to fully characterize the serious risk of interest because:**

*[Select all that apply then go to Q.4.d ]*

- Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- Other

*Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.*

<sup>6</sup> FDA Adverse Event Reporting System (FAERS)

<sup>7</sup> Active Risk Identification and Analysis (ARIA)

d. **The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because:** *[Select all that apply then go to Q.4.e ]*

- Cannot identify exposure to the drug(s) of interest in the database.
- Serious risk (adverse event) of concern cannot be identified in the database.
- The population(s) of interest cannot be identified in the database.
- Long-term follow-up information required to assess the serious risk are not available in the database.
- Important confounders or covariates are not available or well represented in the database.
- The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- Other

e. **If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?** *[Select either “Yes” or “No” and provide the appropriate responses.]*

- Yes**, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

- No**, a study is not sufficient *[Select all explanations that apply then go to Q.4.f ]*

- Need to minimize bias and/or confounding via randomization
- Need for placebo control
- Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- Other

f.  **Because a study is not sufficient, a clinical trial is required.** *[Go to Q.5]*

5. **For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?**

*[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]*

**TYPE OF STUDY**

- Drug interaction or bioavailability studies (nonclinical only)
- Epidemiologic (observational) study related to safe drug use
- Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Immunogenicity study (nonclinical)
- Meta-analysis or pooled analysis of previous observational studies
- Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- Pharmacogenetic or pharmacogenomic study
- Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- Quality CMC study (e.g., manufacturing, studies on impurities)
- Quality stability study
- Registry-based observational study
- Other (describe): This open-label, single-arm study will be conducted in HIV-1 infected neonates (birth to 4 weeks) or those at high risk of HIV-1 infection, to assess the pharmacokinetics, safety, and tolerability of age-appropriate dose(s) of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) given in combination.

**TYPE OF CLINICAL TRIAL**

- Combined PK/PD, safety and/or efficacy trial (*PREA\* PMRs only*)
- Dose-response clinical trial
- Dosing trial (e.g., alternative dosing schedule)
- Drug interaction or bioavailability clinical trial (clinical only)
- Immunogenicity trial (clinical)
- Meta-analysis or pooled analysis of previous clinical trials
- Pharmacogenetic or pharmacogenomic clinical trial
- Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- Safety outcomes trial (SOT)\*\*
- Thorough Q-T clinical trial
- Other (describe) \_\_\_\_\_

\* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

\*\* A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

**SECTION D: PMR/PMC Additional Information**

**1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).**

- Yes
- No

**2. This study or clinical trial focuses on the following special population(s) or circumstance(s):**  
*[Select all that apply]*

- For *non-PREA* pediatric studies/trials only: Pediatric population
- Geriatric population
- Lactating/nursing mothers
- Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- Orphan or rare disease population
- Pregnant women
- Racial/ethnic population
- Not applicable

**3. (Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

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**SECTION E: PMR/PMC Development Coordinator Statements<sup>8</sup>**

**1. The PMR/PMC is clear, feasible, and appropriate<sup>9</sup> because: *[Select all that apply]***

- The study/clinical trial meets criteria for a PMR or a PMC.
- The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- The applicant has adequately justified the choice of milestone dates.
- The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

**2.  (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:**

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

**3.  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.**

Refer to DARRTS electronic signature (Deputy Director for Safety)

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<sup>8</sup> This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

<sup>9</sup> See POLICY section of CDER MAPP 6010.9.

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/s/  
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SUZANNE K STRAYHORN  
01/26/2018

POONAM MISHRA  
01/26/2018

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

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

## Memorandum

**Date:** December 28, 2017

**To:** Suzanne Strayhorn, Regulatory Project Manager  
Division of Antiviral Products (DAVP)

**From:** Wendy Lubarsky, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**CC:** Sam Skariah, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for Biktarvy™ (bictegravir, emtricitabine, tenofovir alafenamide) tablets, for oral use

**NDA:** 210251

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In response to DAVP consult request dated June 14, 2017, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA/BLA submission for Biktarvy™ (bictegravir, emtricitabine, tenofovir alafenamide) tablets, for oral use (Biktarvy).

**PI and PPI:** OPDP's comments on the proposed labeling are based on the draft PI and PPI received by electronic mail from DAVP (Suzanne Strayhorn) on December 7, 2017. We have no comments on the PI at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on December 28, 2017.

**Carton and Container Labeling:** OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on November 1, 2017, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Wendy Lubarsky at (240) 402-7721 or [wendy.lubarsky@fda.hhs.gov](mailto:wendy.lubarsky@fda.hhs.gov).

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/s/  
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WENDY R LUBARSKY  
12/28/2017

**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: December 28, 2017

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

Wendy Lubarsky, PharmD  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

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

Drug Name (bictegravir, emtricitabine, tenofovir alafenamide): BIKTARVY (bicetegravir, emtricitabine and tenofovir alafenamide)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 210251

Applicant: Gilead Sciences, Inc.

## 1 INTRODUCTION

On June 12, 2017, Gilead Sciences, Inc. submitted for the Agency's review an original New Drug Application (NDA) 210251 for BIKTARVY (bictegravir, emtricitabine, and tenofovir alafenamide) tablets. This submission proposes an indication as a complete regimen for the treatment of HIV-1 infection in adults who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 3 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of BIKTARVY.

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 June 14, 2017, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for BIKTARVY (bictegravir, emtricitabine, and tenofovir alafenamide) tablets.

## 2 MATERIAL REVIEWED

- Draft BIKTARVY (bictegravir, emtricitabine, and tenofovir alafenamide) PPI received on June 12, 2017 and received by DMPP and OPDP on December 7, 2017.
- Draft BIKTARVY (bictegravir, emtricitabine, and tenofovir alafenamide) Prescribing Information (PI) received on June 12, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 7, 2017.
- Approved ODEFSEY (emtricitabine, rilpivirine, tenofovir alafenamide) comparator labeling dated August 21, 2017.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information 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.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

#### **4 CONCLUSIONS**

The PPI is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

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

Please let us know if you have any questions.

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/s/  
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RUTH I LIDOSHORE  
12/28/2017

WENDY R LUBARSKY  
12/28/2017

BARBARA A FULLER  
12/28/2017

LASHAWN M GRIFFITHS  
12/28/2017

## Clinical Inspection Summary

<b>Date</b>	December 29, 2017
<b>From</b>	Antoine El Hage, Ph.D. Susan Thompson, M.D./ Team Leader Kassa Ayalew, M.D., M.P.H./ Branch Chief
<b>To</b>	Susanne Strayhorn, MS. /Sr. Regulatory Health Project Manager Tanvir Bell, M.D./ Medical/Clinical Reviewer Wendy Carter, D.O. /Team Leader/ CTDL Division of Antiviral Products (DAVP)
<b>NDA #</b>	210251
<b>Applicant</b>	Gileads Sciences, Inc.
<b>Drug</b>	Bictarvy (Bictegravir, Emtricitabine & Tenofovir alafenamide FDC) tablets
<b>NME</b>	Yes
<b>Therapeutic Classification</b>	Priority
<b>Proposed Indication</b>	Treatment of HIV-1 infected individuals who are HIV-1 ART-naïve or virologically suppressed with no known mutations associated with resistance to the individual components of B/F/TAF
<b>Consultation Request Date</b>	June 30, 2017
<b>Summary Goal Date</b>	January 10, 2018
<b>Action Goal Date</b>	February 12, 2018
<b>PDUFA Date</b>	February 12, 2018

### I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Osiyemi, Charest, Koenig, Berhe, Mills, and Dejesus were inspected in support of this NDA. Data from these all inspected sites are acceptable for use in support of the pending application.

The preliminary classification of the five clinical site inspections is No Action Indicated (NAI). The inspection of Dr. Charest revealed a minor informed consent issue. The minor deviation noted for this site would not appear to have a significant effect on safety or efficacy consideration. The final classification for Dr. Charest's site is Voluntary Action Indicated (VAI).

The final classification for the above five sites will be made after receiving and reviewing the EIRs provided by the filed investigators. An addendum summary will be generated if conclusions change upon receipt and review of the pending EIRs.

## II. BACKGROUND

Bictegravir (BIC-GS-9883) is a potent inhibitor of HIV-1 integrase that is being evaluated for the treatment of HIV-1 infections. Antiviral testing has shown that GS-9883 is active against a broad panel of HIV-1 viral lab strains, and in clinical studies. Integrase mutant viruses that are resistant to the INSTIs raltegravir (RAL) and elvitegravir (EVG) remain largely sensitive to GS-9883. The Applicant has co-formulated GS-9883 with the NRTI emtricitabine (FTC) and NtRTI tenofovir alafenamide (TAF) into an FDC single tablet that is suitable for once-daily use. The GS-9883/FTC, F/TAF FDC may provide a potent convenient, tolerable, and practical regimen for the long-term treatment of subjects with HIV infection. Clinical studies demonstrated that co-administration of the fixed-dose combination in subjects treated for 48 weeks was well tolerated and resulted in the reduction of HIV- RNA levels to less than 50 copies/mL at Week 48.

Bictegravir GS-9883 is not approved yet in the U.S. The Applicant has co-formulated B/F/TAF 50/200/25 mg FDC into a single agent administered together as an oral tablet. The use of a fixed-dose combination may have a major impact on the global prevalence and burden of HIV, as it may represent a simple, well-tolerated, highly efficacious treatment for HIV infected subjects.

The Applicant-sponsored three studies submitted in support of the application: Study Protocols GS-US-380-1844, GS-US-380-1489, and GS-US-380-1490 for treatment of HIV-infected subjects.

**Protocol GS-US-380-1844:** “A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Switching from a Regimen of Dolutegravir and ABC/3TC, or a Fixed-Dose Combination (FDC) of ABC/DTG/3TC to a FDC of GS-9883/F/TAF in HIV-1 Infected Subjects who are Virologically Suppressed”

Subjects: 567 subjects enrolled

Sites: 96 centers in U.S., North America, Australia, and Europe

First subject screened: November 11, 2015

Last subject last observation for the primary endpoint: May 9, 2017

The primary objectives of this study were to evaluate the efficacy of switching from a regimen of DTG and ABC/3TC or a fixed dose combination (FDC) of ABC /DTG/3TC to a FDC of GS-9883/F/TAF versus containing (DTG) and ABC/3TC as the FDC ABC/DTG/3TC in virologically suppressed HIV-1 infected subjects as determined by the proportion of subjects with virologic failure (HIV-1 RNA > 50 copies/mL) at Week 48.

This protocol was an international, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy when switching to GS-9883/F/TAF FDC versus DTG +FDC/3TC as the FDC/DTG/3TC in HIV-1 infected subjects who are virologically suppressed (HIV-1 RNA < 50copies /m/L on a stable regimen of (DTG + ABC/3TC or the FDC ABC/DTG/3TC for greater or equal to 3 months prior to screening. Subjects who provided written informed consent and meet all eligibility criteria were randomized in a 1:1 ratio to the following two treatment groups:

- Group 1 (N=260): FDC of GS-9883 50 mg/emtricitabine 200g/tenofovir alafenamide 25mg (GS-9883/F/TAF + placebo) to match FDC of abacavir 600mg/dolutegravir 50 mg/lamivudine 300 mg (ABC/DTG/3TC) administered orally, once daily, without regard to food.
- Group 2 (N=260) : FDC of abacavir 600mg/dolutegravir 50mg/lamivudine 300mg (ABC/DTG/3 TC) QD + placebo to match FDC of GS-9883 50 mg/ emtricitabine 200mg/tenofovir alafenamide 25 mg (GS-9883(F/TAF) administered orally, once daily, without regard to food.

Subjects were treated for at least 48 weeks, and were unblinded after the last subject completed the Week 48 visit, and the Applicant completed the Week 48 analysis. Subjects continued to take their blinded study drug and attended visits every 12 weeks until treatment assignment have been unblinded.

**Protocol GS-US-380-1490:** “A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of GS-9883/Emtricitabine/Tenofovir Alafenamide versus Dolutegravir+Emtricitabine/Tenofovir Alafenamide in HIV-1 Infected, Antiretroviral Treatment Naïve Adults”,

Subjects: 657 subjects enrolled

Sites: 126 centers in U.S., North America, Asia, and Europe

First subject screened: November 11, 2015

Last subject last observation for the primary endpoint: May 12, 2017

The primary objectives of this study were to: 1) evaluate the efficacy of a fixed dose combination(FDC) containing GS-9883/emtricitabine/tenofovir alafenamide (GS9883/F/TAF versus dolutegravir (DTG) + a FDC containing emtricitabine/tenofovir alafenamide (F/TAF) in HIV-1 infected antiretroviral treatment-naïve adult subjects as determined by the achievement of HIV-1 RNA < 50 copies/m/L at Week 48.

This protocol was an international, randomized, double-blind, multicenter, active-controlled study that will evaluate the safety and efficacy of GS-9883/F/TAF FDC versus DTG +FDC of FTC/TAF in HIV-1 infected antiretroviral treatment-naïve adult subjects. Subjects who provide written informed consent and meet all eligibility criteria were randomized in a 1:1 ratio to the following treatment groups:

- Group 1 (N=300): FDC of GS-9883 50 mg/emtricitabine 200g/tenfovir alafenamide 25mg (GS-9883/F/TAF + placebo) to match dolutegravir 50mg and placebo to match FDC of emtricitabine 200mg/tenfovir alafenamide 25 mg (F/TAF) administered orally, once daily, without regard to food.
- Group 2 (N=300) : Dolutegravir 50mg +FDC of /emtricitabine 200g/tenfovir alafenamide 25mg (F/TAF) + placebo to match FDC GS-9883 50 mg/ emtricitabine 200mg/tenfovir alafenamide 25 mg (GS-9883(F/TAF) administered orally, once daily, without regard to food.

Subjects were randomized by HIV-1 RNA level (< 100,000 copies/mL, > 100,000 to < 400,000 copies, or >400,000 copies/mL at screening.

**Protocol GS-US-380-1489:** “A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of GS-9883/Emtricitabine/Tenofovir Alafenamide versus Abacavir/Dolutegravir/Lamivudine in HIV-1 Infected, Antiretroviral Treatment Naïve Adults”

Subjects: 631 subjects enrolled

Sites: 122 Centers in U.S., Canada, Dominican Republic, and Europe

First subject screened: November 13, 2015

Last subject last observation: May 9, 2017

The primary objectives of this study were to evaluate the efficacy of a fixed dose combination (FDC) containing GS-9883/emtricitabine/tenofovir alafenamide (GS9883/F/TAF) versus a FDC containing abacavir/dolutegravir/lamivudine (ABC/DTG/3TC (F/TAF)) in HIV-1 infected antiretroviral treatment-naïve adult subjects as determined by the achievement of HIV-1 RNA levels < 50 copies/mL at Week 48.

This protocol was a randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of GS-9883/F/TAF FDC versus ABC/DTG/3TCFDC + FDC in HIV-1 infected, antiretroviral treatment-naïve adult subjects. Subjects who provided written informed consent and met all eligibility criteria were randomized in a 1:1 ratio to one of the following two treatment groups:

- Group 1 (N=300): FDC of GS-9883 50 mg/emtricitabine 200 g/tenfovir alafenamide 25 mg (GS-9883/F/TAF + placebo to match FDC of abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg (ABC/DTG/2TC) administered orally, once daily, without regard to food.
- Group 2 (N=300) : FDC of abacavir 600 mg/Dolutegravir 50mg/lamivudine 300mg( abc/dtg/3TC + placebo to match FDC GS-9883 50 mg/ emtricitabine 200 mg/tenofovir alafenamide 25 mg (GS-9883(F/TAF) administered orally, once daily, without regard to food.

Subjects were randomized by HIV-1 RNA level < 100,000 copies/mL, > 100,000 to < 400,000 copies, or > 400,000 copies/mL at screening.

The review division requested inspection of six clinical investigators because data from the studies are considered essential to the approval process. These sites were targeted for inspection due to: 1) enrollment of a relatively large number of subjects with a treatment effect that was greater than average, 2) the need to determine if sites conducted the trials ethically and followed GCP regulations, and 3) financial disclosure issues at certain sites.

Four domestic sites covering three protocols and two foreign sites covering two protocols were requested for inspection. Two sites were identified per pivotal trial.

#### **Site Selection for Study Protocols**

Dr. Osiyemi had 74 INDs in the CDER database and no prior history of CDER inspection. This site reported high enrollment with a high response rate, no adverse events reported, and financial disclosure issues.

Dr. Charest had 1 IND in the CDER database and no prior history of CDER inspection. This is a foreign site with high enrollment and a high response rate.

Dr. Koenig had 3 INDs in the CDER database and two prior inspections classified as NAI in 2012 and 2015. This is a foreign site with high enrollment and a high efficacy response rate.

Dr. Berhe had 6 INDs in the CDER database and no prior history of CDER inspection. This site reported low response rates of 86% BIC vs. 75% DTG and a relatively low number of adverse events reported.

Dr. Mills had 92 INDs in the CDER database and one prior CDER inspection: NAI on 5/25/2012. This site had a high enrollment with a high response rate and financial disclosure issues.

Dr. Dejesus had 3 INDs in the CDER database and no prior history of CDER inspection. This site enrolled large number of subjects with a high response rate and financial disclosure issue.

**III. RESULTS (by site):**

<b>Name of CI, Site #, Address, Country if non- U.S. or City, State if U.S.</b>	<b>Protocol # and # of Subjects</b>	<b>Inspection Date</b>	<b>Final Classification</b>
Olayemi Osiyemi, M.D. West Palm Beach, FL 33407 Site #2106	GS-US-380-1489 Enrolled 19	9/25-29/2017	*NAI
Louise Charest, M.D. Montreal, Quebec H21 4P9 Canada Site #11791	GS-US-380-1489 Enrolled 12	9/25-29/2017	VAI
Ellen Koeing, M.D. Santo Domingo, Dominican Republic Site #986	GS-US-380-1490 Enrolled 45	9/18-22/2017	* NAI
Mezgebe Berhe, M.D. Dallas, TX 75246 Site #11678	GS-US-380-1490 Enrolled 14	9/25-29/2017	*NAI
Anthony Mills, M.D. Los Angeles, CA 90069 Site #2728	GS-US-380-1844 Enrolled 24	8/24-9/1/2017	*NAI
Edwin Dejesus, M.D. Orlando, FL 32803 Site #698	GS-US-380-1844 Enrolled 14	8/7-19/2017	* NAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data are unreliable.

\*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

NOTE: Site inspections focused on review of informed consent documents, IRB, ethics committee correspondence, financial disclosures, training records, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, vital signs, subject source documents,

including medical history records, drug accountability, and the use of concomitant medications. Source documents were compared to data listing for primary efficacy endpoints and adverse events reporting.

**1. Olayemi Osiyemi, M.D./Site #2106 / Study GS-US-380-1489**  
West Palm Beach, FL 33407

There were 19 subjects screened, and 19 subjects were enrolled in the study. Three subjects discontinued and the reasons were documented. Subject #1043 discontinued due to pregnancy; Subject #1022 due to a pre-existing renal condition and non-compliance, and Subject #1103 moved to another country. All 19 subjects completed the Week 48 Visit, and all are continuing the study.

The medical records for all subjects were reviewed for informed consent and primary efficacy endpoints. Records were organized and legible. Medical records/source documents were compared to case report forms and data listings for primary efficacy endpoints and adverse event reporting. The audit revealed adequate adherence to the regulations and investigational plan. There were no objectionable conditions noted, and no Form FDA 483 was issued to Dr. Osiyemi.

The data generated by this site appear acceptable. The inspection did not indicate deviations that would impact the acceptability of the data submitted in support of the application.

**2. Louise Charest, M.D./ Site #11791/Study GS-US-380-1489**  
Montreal, Quebec H21 4P9, Canada

There were 16 subjects screened, four subjects were reported as screen failures, 12 subjects were enrolled, and all 12 subjects are continuing the study. The field investigator reported that the primary endpoints were verified at the site. No data integrity issues were found and no safety concerns were noted.

A one-item FDA 483 was issued to Dr. Charest regarding Subject #1140 who was provided and signed an approved updated informed consent document for another study instead of the approved updated informed consent document for Protocol GS-US-380-1489 under investigation. Therefore, study related tests for Weeks 60 and 72 were performed without the updated informed consent. The clinical investigator responded to the FDA 483 in a written response dated 10/17/2017. The finding was isolated. OSI finds her response to be acceptable.

The medical records for all subjects were reviewed. Records were organized and legible. Medical records/source documents were compared to data listings for primary efficacy

endpoints and adverse events reporting. No major deficiencies were observed. The audit revealed adequate adherence to the regulations and investigational plan.

The data generated at Dr. Charest's site for Protocol GS-US-380-1489 in support of clinical efficacy and safety is considered reliable and may be used in support of the pending application.

**3. Ellen Koenig, M.D./ Site #986/Study GS-US-380-1490**  
Santo Domingo, Dominican Republic

There were 52 subjects screened, seven subjects were reported as screen failures, and 45 subjects were enrolled. The medical records for 21 subjects were reviewed. The study is still ongoing none of the subjects completed the study during the inspection.

The field investigator reported that Subject #2440 was randomized on 6/20/2016 and died after Week 48 due to a cancerous abdominal mass.

The medical records/source documents were compared to case report form and data listings for primary efficacy endpoint and adverse event reporting. The inspection revealed adequate adherence to the regulations and investigational plan. There were no objectionable conditions noted, and no Form FDA-483 Inspectional Observations was issued. The field investigator reported that the medical records were organized and legible.

The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Data from this site appear acceptable.

**4. Mezgebe Berhe, M.D./ Site #11678 /Study GS-US-380-1490**  
Dallas, TX 75246

There were 16 subjects screened, two subjects were reported as screen failures, 14 subjects were randomized, and three subjects discontinued and the reasons were documented. Subject #2580 withdrew informed consent, Subject #2182 due to colon cancer/hospitalization, and Subject #2395 due to incarceration. None of the enrolled subjects have completed the study. All 13 subjects are continuing study treatment. The medical records for 13 enrolled subjects were reviewed during the inspection.

The medical records/source documents were compared to case report forms and data line listings and they were consistent. No under-reporting of adverse events was found. The primary efficacy endpoint was verifiable. The inspection revealed adequate adherence to the regulations and investigational plan. There were no objectionable conditions noted, and no Form FDA-483 Inspectional Observations was issued.

The audit did not indicate serious deviations/findings that would impact on the validity/reliability of the submitted data. Data from this site appear acceptable.

**5. Anthony Mills, M.D./ Site #2728/Study GS-US-380-1844**  
Los Angeles, CA 900695

There were 27 subjects screened, three subjects were reported as screen failures, and 24 subjects were enrolled. Three subjects were discontinued and the reasons were documented: one subject withdrew consent and two subjects transferred out to different sites. All 24 enrolled subjects are continuing in the study. The medical records for all subjects were reviewed. No data integrity issues were found and no safety concerns were noted.

The medical records/source documents were compared to case report form and data listings for primary efficacy endpoint and adverse event reporting. No deficiencies were noted.

At the conclusion of the inspection, no FDA 483 was issued to the clinical investigator. However, the ORA investigator noted and discussed with the clinical investigator a few items regarding calibration of the thermometers used in the investigational product storage room, and the review of source document for one subject in a timely manner. The clinical investigator and his staff acknowledged the inspectional findings.

The data generated at Dr. Mill's site in support of clinical efficacy and safety is considered acceptable and may be used in support of the pending application.

**6. Edwin Dejesus, M.D./ Site #698/Study GS-US-380-1844**  
Orlando, FL 32803

There were 15 subjects screened, one subject was reported as a screen failure, and 14 subjects were enrolled. The study is ongoing. None of the enrolled subjects completed the study. The medical records for all subjects were reviewed. No data integrity issues were found and no safety concerns were noted.

The medical records/source documents for 14 subjects were compared to case report form and data listings for primary efficacy endpoints and adverse event reporting. No deficiencies were observed. After the inspection, no FDA 483 was issued to the clinical investigator. However, the ORA investigator noted and discussed with the clinical investigator a few items such as out of window visits and not returning study medication bottles on time.. The clinical investigator and the staff acknowledged the findings.

The data generated at Dr. Dejesus's site in support of clinical efficacy and safety is considered acceptable and may be used in support of the pending application.

{See appended electronic signature page}

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

CONCURRENCE:

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cc:

Central Doc. Rm. NDA 210251  
DAVP /Division Director/Debra Birnkrant  
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OSI/DCCE/ Division Director/Ni Khin  
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew  
OSI/DCCE/GCPAB/Team Leader/Susan Thompson  
OSI/DCCE/GCPAB/Reviewer/Antoine El Hage  
OSI/DCCE/GCP Program Analysts/Yolanda Patague/ Joseph Peacock

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/s/  
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ANTOINE N EL HAGE  
12/04/2017

SUSAN D THOMPSON  
12/04/2017

KASSA AYALEW  
12/04/2017

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**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\*\*\***

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**Date of This Review:** September 11, 2017  
**Requesting Office or Division:** Division of Antiviral Products (DAVP)  
**Application Type and Number:** NDA 210251  
**Product Name and Strength:** Biktarvy  
(bictegravir, emtricitabine, and tenofovir alafenamide)  
tablets  
50 mg/200 mg/25 mg  
**Product Type:** Multi-ingredient Product  
**Rx or OTC:** Rx  
**Applicant/Sponsor Name:** Gilead Sciences, Inc.  
**Submission Date:** June 12, 2017  
**OSE RCM #:** 2017-1144  
**DMEPA Safety Evaluator:** Nasim Roosta, PharmD  
**DMEPA Team Leader:** Otto L. Townsend, PharmD

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## 1 REASON FOR REVIEW

The Division of Antiviral Products (DAVP) requested that we assess the proposed Prescribing Information (PI), Patient Package Insert (PPI) and container label submitted for NDA 210251 from a medication error prospective. The Applicant also submitted carton labeling and container labels for the (b) (4) with this submission.

## 2 MATERIALS REVIEWED

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

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

N/A=not applicable for this review

\*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed PI, PPI, container label, (b) (4) (b) (4) container label and (b) (4) carton labeling to identify deficiencies that may lead to medication errors and to identify other areas that could be improved.

We note that on the container label, there is no designated location for the lot number and expiration date. This is important information that must be present, in order to avoid potentially dangerous administration errors. Both the lot number and expiration date should be included on the container label. In addition, the expiration date should be in the following format: MMMYYYY (e.g., JAN2018) or MMMDDYYYY (e.g., JAN012018).

We also note that the PI, PPI and all labels and labeling contain the proprietary name placeholder, "TRADENAME", but should be updated to reflect the conditionally acceptable proprietary name, Biktarvy.

Our review of the carton labeling and container labels for the (b) (4) determined that the labels and labeling are identical to the commercial products with the exception of the added statement (b) (4)

#### **4 CONCLUSION & RECOMMENDATIONS**

We identified areas of the PI, PPI, container label and the (b) (4) labels and labeling that can be improved to increase clarity and prominence of important information to promote the safe use of this product.

If you have questions or need clarifications, please contact Danyal Chaudhry, OSE Project Manager, at 301-796-3813.

#### **5 RECOMMENDATIONS FOR THE DIVISION**

In both the PI and PPI, update the “TRADENAME” statement to reflect the conditionally acceptable proprietary name, Biktarvy.

##### **5.1 RECOMMENDATIONS FOR GILEAD SCIENCES, INC.**

We recommend the following be implemented prior to approval of this NDA 210251:

1. Ensure both the lot number and expiration date are included on the container labels. Expiration date should be in the following format: MMMYYYY (e.g., JAN2018) or MMMDDYYYY (e.g., JAN012013).
2. On the commercial container label, (b) (4) container label, and (b) (4) (b) (4) carton labeling, replace the proprietary name placeholder, “TRADENAME”, with the conditionally acceptable proprietary name, Biktarvy.

**APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for Biktarvy that Gilead Sciences, Inc. submitted on June 12, 2017.

<b>Table 2. Relevant Product Information for Biktarvy</b>	
<b>Initial Approval Date</b>	N/A
<b>Active Ingredient</b>	Bictegravir, emtricitabine, and tenofovir alafenamide
<b>Indication</b>	Treatment of Human Immunodeficiency Virus-1 (HIV-1) infection
<b>Route of Administration</b>	Oral
<b>Dosage Form</b>	Tablet
<b>Strength</b>	50 mg/200 mg/25 mg
<b>Dose and Frequency</b>	One tablet by mouth once daily
<b>How Supplied</b>	30-count bottle
<b>Storage</b>	(b) (4)

## **APPENDIX B. PREVIOUS DMEPA REVIEWS**

On August 24, 2017, we searched DMEPA's previous reviews using the terms, 'Biktaryv'. Our search did not identify any previous reviews.

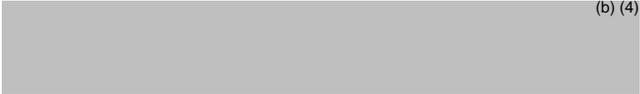
## APPENDIX G. LABELS AND LABELING

### G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>a</sup> along with postmarket medication error data, we reviewed the following Biktarvy labels and labeling submitted by Gilead Sciences, Inc. on June 12, 2017.

- Prescribing Information
- Patient Package Insert
- Container label

(b) (4)



### G.2 Label and Labeling Images

Container label:

(b) (4)



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<sup>a</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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NASIM N ROOSTA  
09/11/2017

OTTO L TOWNSEND  
09/11/2017

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

**Application:** NDA 210251

**Application Type:** Original NDA

**Drug Name(s)/Dosage Form(s):** Proprietary name is under review  
(bictegravir/emtricitabine/tenofovir alafenamide, B/F/TAF), fixed dose combination tablet

**Applicant:** Gilead Sciences, Inc.

**Receipt Date:** June 12, 2017

**Goal Date:** February 12, 2018

### **1. Regulatory History and Applicant's Main Proposals**

On June 12, 2017, the Division of Antiviral Products (DAVP) received an original NDA from Gilead Sciences (Gilead) for bictegravir (BIC/B), emtricitabine (FTC/F), and tenofovir alafenamide (TAF) [B/F/TAF] fixed-dose combination (FDC) tablets for the treatment of HIV-1 infection. The proposed commercial drug product consists of an immediate-release FDC tablet containing 50 mg bictegravir, 200 mg emtricitabine, and 25 mg tenofovir alafenamide to be administered orally, once daily, without food. Gilead states that B/F/TAF is a complete single tablet regimen (STR) proposed to offer reduced pill burden, improved tolerability and renal and bone safety, high rates of durable virologic suppression, fewer drug interactions, and increased options for medical management of patients with multiple and/or complex comorbidities.

The full indication proposed by this applicant for the three-drug fixed dose tablet combination of bictegravir (BIC), an HIV-1 integrase strand transfer inhibitor (INSTI), and emtricitabine (FTC) and tenofovir alafenamide (TAF), both HIV-1 nucleoside analog reverse transcriptase inhibitors (NRTIs), is for the treatment of HIV-1 infection in adults who are HIV-1 (b) (4) associated with resistance to the individual components of the tablet. This application was accompanied by a Tropical Disease Voucher, whereby Priority Review status was granted.

### **2. Review of the Prescribing Information**

This review is based on the applicant's June 12, 2017, submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

### **3. Conclusions/Recommendations**

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

# Selected Requirements of Prescribing Information

## 4. Selected Requirements of Prescribing Information

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The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

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### Highlights

See Appendix for a sample tool illustrating Highlights format.

#### HIGHLIGHTS GENERAL FORMAT

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

**Comment:**

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

**Comment:**

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
  - TOC from the Full Prescribing Information (FPI).

**Comment:**

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

**Comment:**

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

**Comment:**

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

**Comment:**

- YES** 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required

## Selected Requirements of Prescribing Information

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

\* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

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

**Comment:**

#### Highlights Limitation Statement

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

**Comment:**

#### Product Title in Highlights

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

**Comment:**

#### Initial U.S. Approval in Highlights

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

**Comment:** *If approved, 4-digit year will be added*

#### Boxed Warning (BW) in Highlights

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

**Comment:**

- YES** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term

## Selected Requirements of Prescribing Information

“WARNING” and not “WARNINGS” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

**Comment:**

- YES** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

**Comment:**

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

**Comment:**

### Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

**Comment:** *This is a new NDA under review, as such RMC to a pre-existing label does not apply.*

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

**Comment:**

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

**Comment:**

### Dosage Forms and Strengths in Highlights

- N/A** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

**Comment:** *This product has single dosage form as tablets for oral use.*

### Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

## Selected Requirements of Prescribing Information

### Comment:

#### Adverse Reactions in Highlights

- YES** 21. 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 which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

### Comment:

#### Patient Counseling Information Statement in Highlights

- YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

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

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

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

### Comment:

#### Revision Date in Highlights

- YES** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015**”).

Comment: *The date will be added at time of approval.*

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

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

- YES** 24. The TOC should be in a two-column format.  
*Comment:*
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
*Comment:*
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].  
*Comment:*
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
*Comment:*
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS\***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
*Comment:*
-

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Lactation</b> (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use “ <b>Labor and Delivery</b> ”)
<b>8.3 Females and Males of Reproductive Potential</b> (if not required to be in PLLR format, use “ <b>Nursing Mothers</b> ”)
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- YES** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*].”

**Comment:**

## Selected Requirements of Prescribing Information

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

*Comment:*

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

*Comment:*

#### BOXED WARNING Section in the FPI

- YES** 35. All text in the BW should be **bolded**.

*Comment:*

- YES** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

*Comment:*

#### CONTRAINDICATIONS Section in the FPI

- N/A** 37. If no Contraindications are known, this section must state “None.”

*Comment:* *Contraindications are listed.*

#### ADVERSE REACTIONS Section in the FPI

- YES** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

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

*Comment:*

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

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

*Comment:* *This drug has not yet benn approved for marketing.*

## Selected Requirements of Prescribing Information

### PATIENT COUNSELING INFORMATION Section in the FPI

**YES** 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

**Comment:**

**YES** 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:**

# Selected Requirements of Prescribing Information

## Appendix: Highlights and Table of Contents Format

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

**PROPRIETARY NAME** (non-proprietary name) dosage form, route of administration, controlled substance symbol  
Initial U.S. Approval: YYYY

#### WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

### RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y  
Section Title, Subsection Title (x.x) M/201Y

### INDICATIONS AND USAGE

**PROPRIETARY NAME** is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

### DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

### DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

### CONTRAINDICATIONS

- Text (4)
- Text (4)

### WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

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

### DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

### USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

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

Revised: M/201Y

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### WARNING: TITLE OF WARNING

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

#### 6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

#### 7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

#### 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

#### 9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

#### 10 OVERDOSAGE

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

#### 13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

#### 14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SUZANNE K STRAYHORN  
08/07/2017

## 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 #: <b>210251</b>	NDA Supplement #: Not Applicable – Original NDA	Efficacy Supplement Category: Not Applicable not an efficacy supplement <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: Tentatively approved under IND 125589 as BICTARVY Established/Proper Name: bictegravir/emtricitabine/tenofovir alafenamide, B/F/TAF Dosage Form: Tablet Strengths: 50 mg B/ 200 mg F/ 25mg TAF Route(s) of Administration: Oral		
Applicant: Gilead Sciences, Inc. Agent for Applicant (if applicable): N/A		
Date of Application: June 10, 2017 Date of Receipt: June 12, 2017 Date clock started after Unacceptable for Filing (UN): N/A		
PDUFA Goal Date: February 12, 2018	Action Goal Date (if different): N/A	
Filing Date: August 11, 2017	Date of Filing Meeting: July 5, 2017	
Chemical Classification (original NDAs only) : <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input checked="" type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch <input type="checkbox"/> Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) <input type="checkbox"/> Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): Treatment of HIV-1 infection in adults who are HIV-1 <span style="background-color: #cccccc; display: inline-block; width: 150px; height: 1em; vertical-align: middle;"></span> <sup>(b) (4)</sup> associated with resistance to the individual components of B/F/TAF.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: Not Applicable  If 505(b)(2)NDA/NDA Supplement: Draft the “505(b)(2) Assessment” review found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> .	<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)	

Type of BLA: <b>Not Applicable</b>		<input type="checkbox"/> 351(a)		
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>		<input type="checkbox"/> 351(k)		
Review Classification:		<input type="checkbox"/> Standard		
<i>The application will be a priority review if:</i>		<input checked="" type="checkbox"/> Priority		
<ul style="list-style-type: none"> <li>• A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</li> <li>• The product is a Qualified Infectious Disease Product (QIDP)</li> <li>• A Tropical Disease Priority Review Voucher was submitted</li> <li>• A Pediatric Rare Disease Priority Review Voucher was submitted</li> </ul>		<input type="checkbox"/> Pediatric WR		
		<input type="checkbox"/> QIDP		
		<input checked="" type="checkbox"/> Tropical Disease Priority Review Voucher		
		<input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher		
Resubmission after withdrawal? <b>N/A</b>		Resubmission after refuse to file? <b>N/A</b>		
Part 3 Combination Product? <b>N/A</b>		<input type="checkbox"/> Convenience kit/Co-package		
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		<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 type="checkbox"/> Fast Track Designation		<input type="checkbox"/> PMC response: <b>N/A</b>		
<input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i>		<input type="checkbox"/> PMR response: <b>N/A</b>		
<input type="checkbox"/> Rolling Review		<input type="checkbox"/> FDAAA [505(o)]		
<input type="checkbox"/> Orphan Designation		<input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B)		
		<input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41)		
		<input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)		
<input type="checkbox"/> Rx-to-OTC switch, Full				
<input type="checkbox"/> Rx-to-OTC switch, Partial				
<input type="checkbox"/> Direct-to-OTC				
<b>None of the above:</b> (has orphan designation for pediatric indication but that does not apply to current application, which is for adults)				
Other:				
Collaborative Review Division ( <i>if OTC product</i> ): <b>Not Applicable</b>				
List referenced IND Number(s): <b>IND 125589 for bictegrovir, emtricitabine, tenofovir alafenamide; IND 121318 for bictegrovir ; IND 053971, for EMTRIVA (emtricitabine) ; IND 052849 and IND 051285 for VIREAD (tenofovir disoproxil fumarate); IND 103093 for STRIBILD (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate); IND 101283 for cobicistat; IND 063737 for TAF (tenofovir alafenamide); IND 067671 for TRUVADA (emtricitabine, tenofovir disoproxil fumarate) ; IND 111007 for GENVOYA (elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide).</b>				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in the electronic archive?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		<b>Filing:</b> August 11, 2017 <b>74 Day Letter:</b> August 25, 2017 <b>NME Priority Goal:</b> February 11, 2018
<i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>				
Are the established/proper and applicant names correct in electronic archive?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Proprietary name approval pending and not yet added to electronic archive

<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 electronic archive.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a>  <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	PDUFA-V NME, 505(b)(1), Tropical Disease Voucher # 125597 - Used, Priority Review
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Not on AIP List
If yes, explain in comment column.				Not Applicable
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		Not Applicable
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u>  <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 from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment for this application ( <i>check daily email from <a href="mailto:UserFeeAR@fda.hhs.gov">UserFeeAR@fda.hhs.gov</a></i> ):  <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			
<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. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment of other user fees:  <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u>  <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</a>	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> Not Applicable  <input type="checkbox"/> Yes <input type="checkbox"/> No			
<b>505(b)(2)</b> <b>(NDAs/NDA Efficacy Supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application a 505(b)(2) NDA? ( <i>Check the 356h form, cover letter, and annotated labeling</i> ). <b>If yes, answer the bulleted</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Not Applicable not a 505(b)(2)

questions below:																							
<ul style="list-style-type: none"> <li>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> </ul>				<input type="checkbox"/>	<input type="checkbox"/>		N/A																
<ul style="list-style-type: none"> <li>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)].</li> </ul>				<input type="checkbox"/>	<input type="checkbox"/>		N/A																
<ul style="list-style-type: none"> <li>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)]?</li> </ul> <p><i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i></p>				<input type="checkbox"/>	<input type="checkbox"/>		N/A																
<ul style="list-style-type: none"> <li>Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</li> </ul> <p><i>Check the Electronic Orange Book at:</i>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1"> <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													<input type="checkbox"/>	<input type="checkbox"/>		N/A
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																				
<p><i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																							
<ul style="list-style-type: none"> <li>If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement [see 21 CFR 314.50(i)(1)(i)(C) and 314.54]?</li> </ul> <p><i>Check the Electronic Orange Book at:</i>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If no, include template language in the 74-day letter.</b></p> <p><b>Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]</b></p> <p><b>Note: Pharmaceutical equivalents are drug products in identical dosage forms and route(s) of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive</b></p>				<input type="checkbox"/>	<input type="checkbox"/>		N/A																

<i>ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.</i>				
<b>Exclusivity</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a></i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		B/F/TAF granted orphan drug designation on 05/17/2017 (pediatric patients)  DESCOVY (F/TAF) granted orphan drug designation 06/06/2017 (pediatric patients)  The current application is for adults only and does not include pediatric data
<b>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)(14)]?</b>  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>NDAs/NDA efficacy supplements only:</b> Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?  <b>If yes, # years requested: 3 &amp; 5 years and umbrella exclusivity</b>  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	5 years for bictegravir  3 years for the fixed dose combination of bictegravir / emtricitabine/ tenofovir alafenamide  Umbrella exclusivity for tenofovir alafenamide-containing product
<b>NDAs only:</b> Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>If yes, did the applicant:</b> (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>BLAs only:</b> Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?  <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i>  <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Not applicable not a BLA

previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

**Format and Content**

*Do not check mixed submission if the only electronic component is the content of labeling (COL).*

All paper (except for COL)  
 All electronic  
 Mixed (paper/electronic)

CTD  
 Non-CTD  
 Mixed (CTD/non-CTD) – virology next generation sequencing (NGS) datasets submitted on hard drive and uploaded into electronic archive.

**If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?** Not Applicable

**Overall Format/Content**

	YES	NO	NA	Comment
<b>If electronic submission, does it follow the eCTD guidance?<sup>1</sup></b> <b>If not, explain (e.g., waiver granted).</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Next Generation Sequencing virology data submitted separately on hard drive

<b>Index:</b> Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:  <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)  <b>If no, explain.</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?  <b>If yes, BLA #</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Not Applicable – not a BLA
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**Forms and Certifications**

*Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*

**Application Form**

	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<sup>1</sup> <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)]. N/A</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?  <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>  <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Both FDA forms 3454 and 3455 are included with submission
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?  <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>  <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Application is coded with Form 3674
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?  <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>  <i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?  <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i>  <i>If maroon field copy jackets from foreign applicants are</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A – not a paper submission

<i>received, return them to CDR for delivery to the appropriate field office.</i>				
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<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>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not a product with abuse potential
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Triggers PREA – new active ingredient PeRC meeting scheduled for January 10, 2018
<p><b>If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?</b></p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Approved on June 29, 2016 under IND 125589
<p><b>If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</b></p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Pediatric studies were not anticipated at to be included at the time of the submission of this NDA.
<p><b><u>BPCA:</u></b></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<sup>3</sup></i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

2

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

3

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

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<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Submitted 06/20/2017 (SDN 3)
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSL/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (Prescribing Information)(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 labeling <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent labeling <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in Physician Labeling Rule (PLR) format? <sup>4</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not Applicable
<b>For applications submitted on or after June 30, 2015:</b> Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format?  Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	<input checked="" type="checkbox"/>  <input checked="" type="checkbox"/>	<input type="checkbox"/>  <input type="checkbox"/>	<input type="checkbox"/>  <input type="checkbox"/>	  A summary has been included in Clinical Overview (Section 2.5)
<b>For applications submitted on or after June 30, 2015:</b> <b>If PI not submitted in PLLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<sup>4</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>

Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult sent 06/14/17
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? ( <i>send WORD version if available</i> )	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult sent 06/13/2017
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult sent 06/13/2017
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable – Not OTC Product</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		N/A
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> October 21,2015	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Preliminary comments sent on 10/19/2015 & final meeting minutes on 10/28/2015
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> January 26, 2017 (Type C)	<input type="checkbox"/>	<input checked="" type="checkbox"/>		An official Pre-NDA meeting was not held. A Type C (WRO) meeting, with minutes dated 01/26/2017 document

				sagrements and strategy of planned NDA submission
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** July 5, 2017

**BACKGROUND:**

On June 12, 2017, the Division of Antiviral Products (DAVP) received the original NDA from Gilead Sciences (Gilead) for bicitgravir (BIC/B), emtricitabine (FTC/F), and tenofovir alafenamide (TAF) [B/F/TAF] fixed-dose combination (FDC) tablets for the treatment of HIV-1 infection. The proposed commercial drug product consists of an immediate-release FDC tablet containing 50 mg bicitgravir, 200 mg emtricitabine, and 25 mg tenofovir alafenamide to be administered orally, once daily without food. Gilead states that B/F/TAF is a complete single tablet regimen (STR) proposed to offer reduced pill burden, improved tolerability and renal and bone safety, high rates of durable virologic suppression, fewer drug interactions, and increased options for medical management of patients with multiple and/or complex comorbidities. This application was accompanied by a Tropical Disease Voucher, whereby Priority Review status is granted.

Primary studies submitted with this application to support the safety and efficacy of B/F/TAF are two Phase 3 studies of B/F/TAF in HIV-infected, ART naive adult subjects (Studies GS-US-380-1489 and GS-US-380-1490), and two Phase 3 studies of B/F/TAF in HIV-infected, virologically suppressed adult subjects (Studies GS-US-380-1844 and GS-US-380-1878). These data are supported by a Phase 2 study of BIC+ F/TAF in HIV-infected, ART naive adult subjects (Study GS-US-141-1475). These studies were conducted under IND 125589 for B/F/TAF which was opened on May 4, 2015. Information on study design and populations for these studies is presented in the table below.

**Primary Studies to Support Safety and Efficacy of B/F/TAF**

Study	Study Design	Data Presented
<b>HIV-Infected, ART-Naive Adult Subjects</b>		
GS-US-380-1489	Phase 3, randomized, double-blind study to evaluate the safety and efficacy of B/F/TAF vs ABC/DTG/3TC	Week 48 efficacy, PK, and safety
GS-US-380-1490	Phase 3, randomized, double-blind study to evaluate the safety and efficacy of B/F/TAF vs DTG+F/TAF	Week 48 efficacy, PK, and safety
GS-US-141-1475	Phase 2, randomized, double-blinded study to evaluate the safety and efficacy of BIC+F/TAF vs DTG+F/TAF <sup>a</sup> Open-label extension phase allowed crossover from DTG+F/TAF to B/F/TAF or continuation of BIC+F/TAF as the B/F/TAF FDC	<u>Double-blinded phase:</u> Week 48 efficacy, PK, and safety <u>Open-label extension phase:</u> Week 72 efficacy and safety
<b>HIV-Infected, Virologically Suppressed Adult Subjects</b>		
GS-US-380-1844	Phase 3, randomized, double-blind study to evaluate the safety and efficacy of switching to B/F/TAF from DTG+ABC/3TC or ABC/DTG/3TC vs continuing DTG and ABC/3TC as the ABC/DTG/3TC FDC	Week 48 efficacy, PK, and safety
GS-US-380-1878	Phase 3, randomized, open-label study to evaluate the safety and efficacy of switching to B/F/TAF vs continuing on boosted ATV or DRV plus either FTC/TDF or ABC/3TC	Week 48 efficacy, PK, and safety

a The double blind phase of Study GS-US-141-1475 evaluated BIC (75 mg) compared with DTG (50 mg), each administered with F/TAF (200/25 mg). During open-label treatment, subjects received B/F/TAF (50/200/25 mg) FDC tablet.

Gilead holds IND 121318 for bicitgravir (BIC) as a single component (IND opened on April 28, 2014) and this submission includes data for studies conducted under this IND. In addition this submission includes or cross references data for studies conducted for TAF, F/TAF, GENVOYA® (GEN), FTC, and/or FTC/tenofovir disoproxil fumarate (TDF).

## **Regulatory History of Note**

### End of Phase 2

A Type B, End of Phase 2 (EOP2) meeting was held on October 21, 2015, under IND 125589. At the time of this meeting the adequacy of the completed and planned non-clinical studies was discussed. Refer to Preliminary Comments dated October 19, 2015 and finalized Meeting Minutes dated October 28, 2015.

### Agreed iPSP

Under IND 125589, an agreed Pediatric Study Plan was finalized on June 29, 2016 for use of B/F/TAF in children and adolescents 4 weeks of age and older. Gilead requested a waiver for children < 4 weeks of age because necessary studies are impossible or highly impracticable.

### Fast Track Request

Under IND 125589, Gilead placed a request for Fast-Track designation on November 11, 2016, which was denied by the Division as Gilead had not established that B/F/TAF regimen improves virologic outcomes, improves adherence, or is effective in patients with INSTI- resistance as this population has not been studied. In effect there was insufficient data to show potential (given its stage of development) for B/F/TAF to address an unmet medical need.

### Pre-NDA Meeting Request

Under IND 125589, Gilead placed a request for a Pre-NDA meeting on November 4, 2016. The Division reviewed the request and questions from this sponsor and denied the meeting on November 11, 2016, as there was insufficient data submitted to this IND to facilitate constructive discussions relative to the questions being asked by this sponsor. The Division recommended that Gilead place their request for a Pre-NDA meeting at a later date and separately request a Type C meeting to address their questions related to the content and format of the planned NDA submission. It is noted here that no Pre-NDA meeting took place in advance of the NDA submission, which was received June 12, 2017..

### Type C Meeting

Under IND 125589, Gilead placed a request for a Type C meeting on November 21, 2016 to discuss the content and format of their planned NDA. The Division provided final written responses January 26, 2017. The only agreement reached for late NDA submission was for the final clinical study report for a 104 week oral gavage carcinogenicity study in the rat; no submission date was specified in the written responses.

(b) (4)

**REVIEW TEAM:**

<b>Discipline/Organization</b>	<b>Names</b>		<b>Present at filing meeting? (Y or N)</b>
Regulatory Project Management	RPM:	Alicia Moruf (on behalf of Suzanne Strayhorn)	Y
	CPMS/TL:	Elizabeth Thompson	Y
Cross-Discipline Team Leader (CDTL)	Wendy Carter		Y
Division Director/Deputy	Debra Birnkrant		Y
	Jeffrey Murray		Y
Office Director/Deputy	Edward Cox		N
	John Farley		Y
Clinical	Reviewer:	Tanvir Bell	Y
	TL:	Wendy Carter	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:	N/A – not OTC	N/A
	TL:	N/A	N/A
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	Sung Rhee	Y
	TL:	Julian O’Rear	Y
Clinical Pharmacology	Reviewer:	Vikram Arya	Y
	TL:	Islam Younis	N
• Genomics	Reviewer:		N/A
• Pharmacometrics	Reviewer:		N/A
Biostatistics	Reviewer:	Wen Zeng	Y
	TL:	Thamban Valappil	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	John Dubinion Mark Powley presented	N Y
	TL:	Hanan Ghantous	Y
Statistics (carcinogenicity)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Product Quality (CMC) Review Team:	ATL:	Andrei Ponta (Steve Miller)	Y Y
	RBPM:	Luz Rivera	N
• Drug Substance	Reviewer:	Gaetan Ladouceur	N
• Drug Product	Reviewer:	Yong Wang	N
• Process	Reviewer:	Ying Wang	N
• Microbiology	Reviewer:		
• Facility	Reviewer:	TBD – TL Derek Smith	
• Biopharmaceutics	Reviewer:	Gerlie Gieser	Y
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:	N/A – not a BLA	N/A
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	Ruth Lidoshore	N
	TL:	Barbara Fuller	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Wendy Lubarsky	N
	TL:	Sam Skariah	N
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Nasim Roosta	N
	TL:	Otto Townsend	N
OSE/DRISK (REMS)	Reviewer:	Naomi Redd	N
	TL:	Elizabeth Everhart	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Anthony El Hage	N
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Other reviewers/disciplines			
<ul style="list-style-type: none"> <li><b>Discipline</b></li> </ul> <p><small>*For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"</small></p>	Reviewer:		
	TL:		
Other attendees			
<small>*For additional lines, right click here and select "insert rows below"</small>			

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>505(b)(2) filing issues: <ul style="list-style-type: none"> <li>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p> </li> </ul>	<input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments

<p><b>CLINICAL</b></p> <p><b>Comments:</b></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"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></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"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><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></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason: This NDA received a priority review under PDUFA V due to a tropical disease voucher and was not presented at the Antiviral Products Advisory Committee because BCV is the fourth member of the INSTI drug class. An advisory committee meeting was not warranted for the following reasons [Reference is made to the Draft Guidance for the Public and FDA Staff on Convening Advisory Committee Meetings, August 2008]: <ul style="list-style-type: none"> <li>BCV is neither first-of-a-kind, first-in-class medical product nor a medical product for a significant new indication. BCV is the fourth INSTI and 40 agents (single and fixed dose combinations) are approved for the treatment of HIV infection, thus not a new indication.</li> <li>BCV is not a novel product or use of new technology</li> <li>The review team's preliminary assessment based on the pre NDA package of the risk/benefit ratio is not controversial and risks and benefits appear similar to the approved INSTI class. In general, the safety concerns appear typical for HIV drugs and studied patient population.</li> <li>The review team has not identified any significant questions or concerns about how the trials conducted nor identified any significant differences of scientific opinion on the preliminary trial results.</li> <li>Finally, the efficacy and safety results and labeling have presented similar issues the Division has dealt with in past applications and can be addressed within the Agency and do not require outside expertise.</li> </ul>
<ul style="list-style-type: none"> <li>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</li> </ul>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

health significance?  <b>Comments:</b>	
<b>CONTROLLED SUBSTANCE STAFF</b> • Abuse Liability/Potential  <b>Comments:</b>	<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
<b>CLINICAL MICROBIOLOGY</b>  <b>Comments:</b>	<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

<b>CLINICAL PHARMACOLOGY</b>  <b>Comments:</b>	<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
• Clinical pharmacology study site(s) inspections(s) needed?	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>BIOSTATISTICS</b>  <b>Comments:</b>	<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
<b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b>  <b>Comments:</b>	<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
<b>PRODUCT QUALITY (CMC)</b>  <b>Comments:</b>	<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
<b><u>New Molecular Entity (NDAs only)</u></b>  • Is the product an NME?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b><u>Environmental Assessment</u></b>  • Categorical exclusion for environmental assessment	<input checked="" type="checkbox"/> YES

<p>(EA) requested?</p> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> </ul> <p><b>Comments:</b> There are 19 facilities in this application. It is proposed to submit 1 Facility IR (request BIC DS executed batch records and comparison of BIC DS manufacturing process for Gilead Alberta vs. Esteve Huayi).</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>CMC Labeling Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>If so, were the late submission components all submitted within 30 days?</li> </ul>	<p><input type="checkbox"/> N/A</p> <p><input checked="" type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>What late submission components, if any, arrived after 30 days?</li> </ul>	

<ul style="list-style-type: none"> <li>Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<b>REGULATORY PROJECT MANAGEMENT</b>	
<p><b>Signatory Authority:</b> Office Level (Ed Cox/John Farley)  <b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): September 14, 2017 (internal) &amp; September 25, 2017 with applicant</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):</p> <p><b>Comments:</b></p>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.  <input type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review  <input checked="" type="checkbox"/> Priority Review</p>
<b>ACTION ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<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 checked="" type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input checked="" type="checkbox"/>	Other Office signatory authority was not yet decided as of July 11, 2017 at Admin Rounds.

Annual review of template by OND ADRAAs completed: April 2016

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ALICIA MORUF  
07/11/2017

ELIZABETH G THOMPSON  
07/12/2017