CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204790Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

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

NDA/BLA # 204790
Product Name: Tivicay (dolutegravir)

PMR/PMC Description: Conduct a trial to evaluate pediatric pharmacokinetics, safety and antiviral activity of dolutegravir in HIV-1 infected integrase strand transfer inhibitor-naïve, pediatric subjects 4 weeks to less than 12 years of age. Initial evaluation of dolutegravir exposure must be performed in an initial pharmacokinetic study or substudy to allow dose selection. Using doses selected based on the pharmacokinetic study/substudy, and agreed upon with the FDA, conduct a longer-term pediatric safety and antiviral activity assessment of dolutegravir plus background regimen assessing activity on the basis of continued HIV-1 RNA virology response and safety monitoring over at least 24 weeks of dosing.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	completed
Study/Trial Completion:	05/31/2018
Final Report Submission:	09/30/2018

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

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

The application for dolutegravir use in adults and in integrase strand transferase inhibitor (INSTI)-naïve pediatric ages 12-18 years is ready for approval. Trials in the remaining pediatric age groups are not completed therefore the PMR is being issued under Pediatric Research Equity Act (PREA). This PMR requires the Applicant to conduct a trial in the specified age groups and submit data to FDA for pediatric dosing recommendations.

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

The review issue is pharmacokinetic activity, safety, and antiviral activity of dolutegravir in the INSTI-naïve pediatric subjects ages 4 weeks to less than 12 years.

The goal of the trial is to evaluate pharmacokinetic, safety, and antiviral activity data of dolutegravir in pediatric ages 4 weeks to less than 12 years of age. These data are intended to support dolutegravir dosing recommendations in the pediatric age groups.

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

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

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
  - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

Required

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

Continuation of Question 4

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

Agreed upon:

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

☐ Other

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

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

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

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

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

PMR/PMC Development Coordinator:

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

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/s/

SOHAIL MOSADDEGH
08/08/2013

PMR/PMC Development Template

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

NDA/BLA # 204790
Product Name: Tivicay (dolutegravir)

PMR/PMC Description: Conduct a trial to evaluate pediatric pharmacokinetics, safety and antiviral activity of dolutegravir in HIV-1 infected subjects, ages 2 years to less than 18 years, who are integrase strand transfer inhibitor (INSTI) experienced with certain INSTI associated resistance substitutions or clinically suspected INSTI resistance. Initial evaluation of dolutegravir exposure must be performed in an initial pharmacokinetic study or substudy to allow dose selection. Using doses selected based on the pharmacokinetic study/substudy, and agreed upon with the FDA, conduct a longer-term pediatric safety and antiviral activity assessment of dolutegravir plus background regimen assessing activity on the basis of continued HIV-1 RNA virology response and safety monitoring over at least 24 weeks of dosing.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	06/30/2016
	Study/Trial Completion:	06/30/2022
	Final Report Submission:	01/31/2023

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

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

The application for dolutegravir in adults with documented or clinically suspected integrase strand transfer inhibitor (INSTI)-resistance is ready for approval; however, pediatric study in this population has not been initiated. The efficacy and safety of dolutegravir in INSTI-resistant adults was not established until review of adult trial data in this NDA. We are deferring the pediatric study in this population because data in pediatric subjects are not available at this time. The PMR will be issued under the Pediatric Research Equity Act (PREA) requiring the Applicant to conduct trials and submit data to FDA for pediatric dosing recommendations.

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

The review issue is pharmacokinetic activity, safety, and antiviral activity of dolutegravir in pediatric subjects ages 2 years to less than 18 years with documented or clinically suspected INSTI resistance.

The goal of the trial is to evaluate pharmacokinetic, safety, and antiviral activity data of dolutegravir in pediatric ages 2 years to less than 18 years of age. These data are intended to support pediatric dosing recommendations for population with documented or clinically suspected INSTI resistance.

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

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

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
  - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

Open-label study evaluating pharmacokinetic activity, safety, and antiviral activity of dolutegravir in pediatric subjects ages 2 years to less than 18 years with documented or clinically suspected INSTI resistance.

Required

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

Continuation of Question 4

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

Agreed upon:

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

☐ Other

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

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

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

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

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

PMR/PMC Development Coordinator:

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

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/s/

SOHAIL MOSADDEGH
08/08/2013

PMR/PMC Development Template

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

NDA/BLA # 204790
Product Name: Dolutegravir, Tivicay

PMR/PMC Description: Submit the final report for 48 week data analyses which should include, but not be limited to safety analyses of hepatic, renal and hypersensitivity events, and resistance substitutions from trial ING111762 in treatment-experienced, integrase strand transfer inhibitor-naïve subjects.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	completed
Study/Trial Completion:	completed
Final Report Submission:	03/2014

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

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

The approval of dolutegravir in the treatment-experienced, integrase strand transferase inhibitor (INSTI)-naïve population is adequately supported by 24-week safety and efficacy data. The Division, however, is requiring submission of longer duration safety data up to 48 weeks from this trial.

The main safety concerns with dolutegravir include hypersensitivity reactions, hepatic enzyme elevations, and renal events. Serious and potentially life-threatening hypersensitivity reactions including cases with hepatic involvement were observed in clinical trials. The Tivicay label will carry a warning for this event. Hepatic enzyme elevations of grade 3 or 4 severity were observed in subjects with hepatitis B and/or C coinfection. Enzyme elevations were attributed to hepatitis virus reactivation or immune reconstitution syndrome, although hepatotoxicity was not definitively excluded in some cases. The risk for hepatic enzyme elevations will also be conveyed in the label under Warnings/Precautions. Renal laboratory abnormalities and adverse events were observed in clinical trials, although based on the available data no warning is warranted in the label at present. The Division's primary concern is new-onset or worsening toxicity with longer cumulative exposure, particularly for hepatic and renal-related toxicities, and therefore we are requiring submission of 48 week safety data. These data are intended to further characterize the drug safety profile in the treatment-experienced INSTI-naïve population.

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

The specific review issue is 48-week safety of dolutegravir in treatment-experienced, INSTI -naive subjects. As noted in response to question #1 above, the goal is to further characterize safety with drug use over a longer period of use.

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

- **Which regulation?**

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

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

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

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

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

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

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

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

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

A randomized, double-blind trial to evaluate the safety and efficacy of dolutegravir in treatment-experienced, INSTI-naïve HIV-infected subjects.

Required

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

Continuation of Question 4

☒ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
Week 24 data were submitted from ING111762 to support approval. The PMR will ensure submission of 48-week safety data from this trial.

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

Agreed upon:

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

☐ Other

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

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

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

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

☐ There is a significant question about the public health risks of an approved drug
☒ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation

☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

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

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/s/

SOHAIL MOSADDEGH
08/08/2013

PMR/PMC Development Template

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

NDA/BLA # 204790
Product Name: Dolutegravir, Tivicay

PMR/PMC Description: Submit the final report for 48 week data analyses which should include, but not be limited to safety analyses of hepatic, renal and hypersensitivity events, and resistance substitutions from study ING112574 in treatment-experienced, integrase strand transfer inhibitor-experienced subjects.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	completed
	Study/Trial Completion:	01/2014
	Final Report Submission:	03/2014

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

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

The approval of dolutegravir in the treatment-experienced integrase strand transferase inhibitor (INSTI)-experienced population is adequately supported by 24-week safety and efficacy data. The Division, however, is requiring submission of longer duration safety data up to 48 weeks from this trial.

The main safety concerns with dolutegravir include hypersensitivity reactions, hepatic enzyme elevations, and renal events. Serious and potentially life-threatening hypersensitivity reactions including cases with hepatic involvement were observed in clinical trials. The Tivicay label will carry a warning for this event. Hepatic enzyme elevations of grade 3 or 4 severity were observed in subjects with hepatitis B and/or C coinfection. Enzyme elevations were attributed to hepatitis virus reactivation or immune reconstitution syndrome, although hepatotoxicity was not definitively excluded in some cases. The risk for hepatic enzyme elevations will also be conveyed in the label under Warnings/Precautions. Renal laboratory abnormalities and adverse events were observed in clinical trials, although based on the available data no warning is warranted in the label at present. The Division's primary concern is new-onset or worsening toxicity with longer cumulative exposure, particularly for hepatic and renal-related toxicities, and therefore we are requiring submission of 48 week safety data. These data are intended to further characterize the drug safety profile in the treatment-experienced INSTI-experienced population.

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

The specific review issue is 48-week safety of dolutegravir in treatment-experienced, INSTI -experienced subjects. As noted in response to question #1 above, the goal is to further characterize safety with drug use over a longer period of use.

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

- **Which regulation?**

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

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

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

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

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

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

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

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

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

An open-label, single arm trial in treatment-experienced, INSTI-experienced subjects. The non-comparator design is acceptable because the enrolled population is heavily treatment-experienced with limited antiretroviral options. As mentioned previously, 24 week data from the trial supported drug approval, and the focus of this PMR is submission of 48 week safety data.

Required

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

Continuation of Question 4

☒ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
Week 24 data were submitted from study ING112574 to support approval. The PMR will ensure submission of 48 week safety data from this trial.

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

Agreed upon:

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

☐ Other

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

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

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

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

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation

☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

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

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/s/

SOHAIL MOSADDEGH
08/08/2013

PMR/PMC Development Template

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

NDA/BLA # 204790
Product Name: Tivicay (dolutegravir)

PMR/PMC Description: Submit the final report for 48 week data analyses from the ongoing trial ING116529 (Viking-4) evaluating dolutegravir 50 mg twice daily.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	completed
	Study/Trial Completion:	07/2014
	Final Report Submission:	10/2014

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

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

Data from study ING112574 submitted in the original NDA provide adequate evidence of efficacy and safety of dolutegravir to support approval in the treatment-experienced integrase (INSTI)-experienced population. The Applicant is conducting another trial ING116529 in the INSTI-experienced population (b) (4) [redacted] We are issuing this PMC in order to have the opportunity to review data from ING116529.

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

As mentioned under #1, (b) (4) [redacted] PMC is being issued to ensure that data from trial ING116529 are submitted for FDA review.

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

   - **Which regulation?**

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

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

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

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

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

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

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

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

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

An open-label randomized trial of dolutegravir in treatment-experienced, INSTI-experienced subjects.

Required

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

Continuation of Question 4

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

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

Agreed upon:

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

☒ Other
Submission of a final report for atatrial ING116529 to confirm efficacy in this population.

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

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

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

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/s/

SOHAIL MOSADDEGH
08/08/2013

PMR/PMC Development Template: Product Quality (CMC)

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

NDA/BLA #	NDA 204-790
Product Name:	
PMC #1 Description:	PMC for Study to Validate Sensitivity of Drug Quality Analytical Procedures for Potential (b) (4) Degradants

PMC Schedule Milestones:		
	Final Protocol Submission:	NA
	Study/Trial Completion:	NA
	Final Report Submission:	NA
	Other: Submit CBE-0 Manufacturing Supplement	03/31/2014

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS *FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL.*USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- ***DO NOT USE THIS FORM* IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALY REPORTABLE**

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

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

Concern was identified during NDA review, and testing by the FDA laboratory (St. Louis) confirmed that applicant needs to conduct additional validation of the analytical procedures for measuring impurities in the drug substance and drug product.

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

Insufficient validation was provided in the CMC portions of the NDA with regard to (b) (4) degradation. Additional validation study of two analytical procedures that are used for quality control is needed. Specifically, a laboratory study is needed to demonstrate that the analytical procedures can detect any degradants (b) (4) if they were to form in the dolutegravir sodium drug substance or the dolutegravir tablets.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

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

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

   Describe the agreed-upon study:

As submitted in the May 14, 2013 amendment to NDA 204-790 (EDR-023):
In alignment with the Agency's guidance at the 10May2013 teleconference, as a Post-Marketing Commitment the sponsor agrees to:
Conduct the requested (b) (4) testing for drug substance to target (b) (4) degradation, evaluate both drug substance and drug product impurities methods using these conditions, and submit the data as a Changes Being Effected in 0 Days Supplement to be filed within 6 months from the date of NDA action.

5. To be completed by ONDQA/OBP Manager:

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

PMR/PMC Development Coordinator:

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

_____

(signature line for BLAs only)

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/s/

SOHAIL MOSADDEGH
08/08/2013

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

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

Memorandum

Date: **June 10, 2013**

To: **Sohail Mosaddegh, PharmD, Regulatory Project Manager**
Division of Antiviral Products

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

Subject: **NDA 204790**
TIVICAY (dolutegravir) Tablets for Oral Use

As requested in the Division of Antiviral Products' (DAVP) consult dated January 2, 2013, the Office of Prescription Drug Promotion (OPDP) has reviewed the TIVICAY prescribing information, carton/container labeling, and patient package insert.

OPDP's comments on the prescribing information and carton/container labeling were provided under separate cover on June 6, 2013.

OPDP reviewed the proposed patient package insert sent via email by the Division of Medical Policy Programs on June 7, 2013, and has no comments at this time.

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

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/s/

JESSICA M FOX
06/10/2013

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

PATIENT LABELING REVIEW

Date:	June 7, 2013
To:	Debra B. Birnkrant, MD Director Division of Antiviral Products (DAVP)
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Nathan Caulk, MS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	TIVICAY (dolutegravir)
Dosage Form and Route:	Tablets for Oral Use
Application Type/Number:	NDA 204-790
Applicant:	ViiV Healthcare Company c/o GlaxoSmithKline, LLC

1 INTRODUCTION

On December 17, 2012,ViiV Healthcare Company submitted for the Agency's review a 505(b) New Drug Application (NDA) 204-790 for TIVICAY (dolutegravir) tablets. The Applicant proposes the following indication for TIVICAY (dolutegravir) tablets: in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and children aged12 years and older.

On January 2, 2012, the the Division of Antiviral Products (DAVP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for TIVICAY (dolutegravir) Tablets.

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

2 MATERIAL REVIEWED

- Draft TIVICAY (dolutegravir) Tablets Patient Package Insert (PPI) received on December 17, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on May 28, 2013.
- Draft TIVICAY (dolutegravir) Tablets Prescribing Information (PI) received on December 17, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on May 28, 2013.
- Approved EDURANT (rilpivirine) comparator labeling dated December 7, 2012.

3 REVIEW METHODS

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

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

In our review of the PPI we have:

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

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

NATHAN P CAULK
06/07/2013

SHARON R MILLS
06/07/2013

LASHAWN M GRIFFITHS
06/07/2013

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

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

Memorandum

Date: **June 6, 2013**

To: **Sohail Mosaddegh, PharmD, Regulatory Project Manager**
Division of Antiviral Products

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

Subject: **NDA 204790**
TIVICAY (dolutegravir) Tablets for Oral Use

As requested in the Division of Antiviral Products' (DAVP) consult dated January 2, 2013, the Office of Prescription Drug Promotion (OPDP) has reviewed the TIVICAY prescribing information, carton/container labeling, and patient package insert.

OPDP's comments are provided directly below in the proposed substantially complete version of the prescribing information sent by DAVP via email on May 24, 2013.

OPDP has no comments on the carton/container labeling obtained from EDR Location: \\CDSESUB1\EVSPROD\NDA204790\204790.enx.

OPDP's comments on the patient package insert will be sent under separate cover.

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

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/s/

JESSICA M FOX
06/06/2013

M E M O R A N D U M

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

DATE: May 29, 2013

TO: Debra B. Birnkrant, M.D.
Director
Division of Antiviral Products

and

John A. Lazor, Pharm.D.
Director
Division of Clinical Pharmacology 4
Office of Clinical Pharmacology

FROM: Gopa Biswas, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, R.Ph., Ph.D.
Chief
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

and

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIRs covering NDA 20479, Dolutegravir (DTG, GSK1349572) sponsored by GSK/ViiV Healthcare

At the request of Division of Antiviral Products (DAVP) and Division of Clinical Pharmacology 4 (DCP4), the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted an inspection of the analytical portion of the following pediatric pharmacokinetic study:

Study Number: ING112578 (2001N130479_00)
Study Title: "P1093: Phase I/II, Multi-Center, Open-Label Pharmacokinetic, Safety, Tolerability and Antiviral Activity of GSK1349572, a Novel Integrase Inhibitor, in Combination Regimens in HIV-1 Infected Infants, Children and Adolescents."

The analytical data for the study were audited by ORA investi (b) (4) st Gopa (b) (4)

The audits included a thorough review of study records, electronic data, examination of facilities, equipment, and interviews and discussions with the firm's management and staff.

At the conclusion of the inspection, a Form FDA-483 containing inspectional observations was issued (**Attachments 1**).

The principal investigator (PI) (b) (4) submitted his response to the inspectional observations in electronic form on May 28, 2013 (**Attachment 2**). DBGLPC provides the evaluation of the inspectional observations and the response below:

OBSERVATION 1

(b) (4)

(b) (4)

OBSERVATION 2

(b) (4)

OBSERVATION 3

(b) (4)

(b) (4)

[redacted]

Conclusion:
Following evaluation of the inspectional observations and the firm's response, DBGLPC recommends that analytical data for study ING112578 (IMPAACT Study-P1093) be accepted for further Agency review.

Gopa Biswas, Ph.D.
Bioequivalence Branch, DBGLPC, OSI

Final Classification:

VAI: (b) (4)

FEI: (b) (4)

CC:
CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Dejernett
DBGLPC/BeB/Haidar/Choi/Biswas
OND/OAP/DCP4/DAVP/Mosaddegh/Birnkrant
OTS/ r
ORA (b) (4)
Draft: GB 05/13/2013
Edit: YMC 05/28/2013; SHH 05/29/2013; WHT 05/29/2013
BE File # 6417; O:\BE\EIRCOVER\204790gsk.dol.doc
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/Electronic Archive/BEB
FACTS: 1494900

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/s/

GOPA BISWAS
05/29/2013

SAM H HAIDAR
05/29/2013

WILLIAM H TAYLOR
05/30/2013

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

Label, Labeling and Packaging Review

Date:	May 22, 2013
Reviewer:	Morgan Walker, Pharm.D., MBA Division of Medication Error Prevention and Analysis
Team Leader:	Jamie Wilkins Parker, Pharm.D. Division of Medication Error Prevention and Analysis
Associate Director:	Scott Dallas, RPh. Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Tivicay (Dolutegravir) Tablets, 50 mg
Application Type/Number:	NDA 204790
Applicant:	ViiV Healthcare
OSE RCM #:	2012-2992

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

Contents

1 INTRODUCTION

This review evaluates the proposed container label and package insert labeling for Tivicay (Dolutegravir) Tablets, 50 mg (NDA 204790) for areas of vulnerability that could lead to medication errors.

1.1 PRODUCT INFORMATION

The following product information is provided in the December 17, 2012 submission.

- Active Ingredient: Dolutegravir
- Indication of Use: Treatment of HIV-1 infection (integrase inhibitor)
- Route of Administration: Oral
- Dosage Form: Tablets
- Strength: 50 mg
- Dose: 50 mg once daily in combination with other ART agents in therapy naïve patients and therapy experienced, integrase naïve patients, and 50 mg twice daily in combination with other ART agents in therapy experienced, integrase experienced patients.
- How Supplied: Bottles of 30 tablets
- Storage: Store at 25°C (77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

2 METHODS AND MATERIALS REVIEWED

DMEPA reviewed the Tivicay labels and package insert labeling submitted by the Applicant.

2.1 LABELS AND LABELING

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

- Container Label submitted December 17, 2012 (Appendix A)
- Insert Labeling submitted December 17, 2012

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our risk assessment of the Tivicay product container label and insert labeling.

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

3.1 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESMENT

We have reviewed the package insert labeling as well as the container label. The package insert labeling is acceptable from a medication error perspective. However, we have identified the following vulnerabilities within the container label that may contribute to medication errors:

- The font size of the proposed proprietary name is inconsistent and may interfere with readability. Presently, the letter 'v' appears to have greater prominence than the letter 'i'. The bar of the letter 'i' should be the same height as the letter 'v'.
- The established name is not prominent enough.
- There is no barcode, lot number, or expiration date on the label.
- The QR code is too prominent and competes with the strength statement and other important information on the principal display panel.
- The net quantity statement is too close to the strength statement.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed container label can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

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

A. Comments to the Applicant

1. Ensure that the font size and style of the proposed proprietary name is consistent throughout so that all small case letters appear to have the same prominence and this presentation of the name does not interfere with readability. Presently, the letter 'v' appears to have greater prominence than the letter 'i'. The bar of the letter 'i' should be the same height as the letter 'v'.

2. Ensure that the established name, active ingredient and dosage formulation are at least ½ size of the proposed proprietary name. Ensure the established name, (dolutegravir) Tablets, has prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printing features per 21 CFR 201.10(g)(2).

3. Ensure that there is a barcode, lot number and expiration date on the label per 21 CFR 201.17 and 201.25.

4. Relocate the QR code from the principal display panel of the container label to the side panel. Ensure that the QR code is placed away from the bar code and in a size that does not compete with or distract from the presentation of other required information on the label.

5. Relocate the net quantity statement (i.e. 30 tablets) below the "Each film-coated tablet…" statement to help prevent confusion between the strength and net quantity statements.

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

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

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

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

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

Appendix B: Container Labels

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/s/

MORGAN A WALKER
05/22/2013

JAMIE C WILKINS PARKER
05/22/2013

SCOTT M DALLAS
05/22/2013

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: May 13, 2013

TO: Sohail Mosaddegh Pharm.D., Regulatory Health Project Manager
Charu Mullick M.D., Medical Officer
Division of Antiviral Products

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

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

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

SUBJECT: Evaluation of Clinical Inspections

NDA: 204-790

APPLICANT: GlaxoSmithKline, Inc.

DRUG: Dolutegravir (GSK1349572)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority review
INDICATION: Treatment of HIV-1 infection
CONSULTATION REQUEST DATE: February 6, 2013
DIVISION ACTION GOAL DATE: August 16, 2013
PDUFA DATE: August 17, 2013
INSPECTION SUMMARY: June 16, 2013

I. BACKGROUND:

The sponsor, GlaxoSmithKline LLC., submitted NDA 204790 for TIVICAY (dolutegravir) tablets on behalf of ViiV Healthcare. GSK conducted the studies in support of the marketing approval of dolutegravir in the treatment of HIV infection in adults and pediatric patient aged 12 years of age and older. GlaxoSmithKline sold the IND to ViiV in 2010 and remains responsible for implementing and managing all aspects of these studies. Dolutegravir (DTG, GSK1349572) is an orally administered integrase inhibitor being developed for the treatment of HIV infection. The clinical studies supporting this program were conducted under IND 075382: ING113086 (SPRING-2), ING114467 (SINGLE), ING112574 (VIKING-3), and 111762 (SAILING).

Protocols: Study ING113086/SPRING 2: "A Phase III, Randomized, Double-Blind Study of the Safety and Efficacy of GSK 1349572 50mg Once Daily Compared to Raltegravir (RAL) 400mg Twice Daily Both Administered with Fixed-Dose Dual Nucleoside Reverse Transcriptase Inhibitor Therapy Over 96 Weeks in HIV-1 Infected Antiretroviral Therapy Naïve Adult Subjects";

Study ING114467/SINGLE: "A Phase III, Randomized, Double-Blind Study of the Safety and Efficacy of GSK 1349572 Plus Abacavir (ABC)/Lamivudine (3TC) Fixed-Dose Combination (FDC) Therapy Administered Once Daily Compared to Atripla Over 96 Weeks in HIV-1 Infected Antiretroviral Therapy Naïve Adult Subjects";

Study ING112574/VIKING 3: "A Phase III Study to Demonstrate the Antiviral Activity and Safety of Dolutegravir in HIV-1 Infected Adult Subjects with Treatment Failure on an Integrase Inhibitor Containing Regimen" and

Study ING111762/SAILING: "A Phase III, Randomized, Double-Blind Study of the Safety and Efficacy of GSK 1349572 50 mg Once Daily Versus Raltegravir 400mg Twice Daily, Both Administered With an Investigator-Selected Background Regimen Over 48 Weeks in HIV-1 Infected, Integrase Inhibitor-Naïve, Antiretroviral Therapy-Experienced Adults".

Investigational Drug

Dolutegravir (DTG) is a class of antiretroviral (ART) drugs designed to block the action of the integrase viral enzyme which catalyzes several key steps in the HIV life cycle and is responsible for insertion of the viral genome into deoxyribonucleic acid (DNA) of the host cell. The first HIV integrase inhibitors (INI), raltegravir (RAL) was approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in October and December of 2007 respectively.

The studies were conducted to further evaluate a new class of ART drugs, INI, and to demonstrate the potential benefit of DTG *once daily dosing compared to RAL twice daily dosing.* The Applicant states that once daily dose of DTG is well tolerated and efficacious in HIV-1 infected subjects. The applicant is seeking approval of the new product by submitting

data from three pivotal phase III protocols SPRING-2, SINGLE (tx-naïve population), SAILING (tx-experienced population), and VIKING-3 (INI-resistant population). The most common side effects include headache, nausea, diarrhea, hepatotoxicity, hypersensitivity, renal events including increased creatinine, suicidal ideation, confusion, insomnia, CPK elevation, and rhabdomyolysis.

(b) (4)

The Applicant-sponsored pivotal studies were submitted in support of the application. This is a brief summary of the studies:

Study ING 113086/SPRING-2

ING113086 (SPRING-2) is a phase III randomized, double-blind, active-controlled, mulitcenter, non-inferiority study conducted in 822 HIV-1 infected, antiretroviral therapy (ART)-naïve subjects. The study was designed to demonstrate the non-inferior antiviral activity of DTG 50 mg once daily versus RAL 400 mg twice daily, both administered with either abacavir/lamivudine (ABC/3TC), or tenofovir/emtricitabine (TDF/FTC, Truvada) to ART-naïve adult subjects over 96 weeks. The main purpose of the study was to demonstrate the potential benefit of DTG once daily compared to RAL twice daily.

The primary objective of Study ING113086 was to demonstrate the antiviral activity of GSK 1349572 50 mg administered once daily compared to Raltegravir (RAL) 400 mg twice daily over 48 weeks in HIV-1 infected therapy naïve subjects.

The secondary objectives were: 1) to determine the antiviral activity of GSK 1349572 compared to RAL over 96 weeks, and 2) to assess the development of viral resistance in subjects experiencing virological failures.

Study ING114467/SINGLE

ING114467 (SINGLE) is a phase III, randomized, double-blind study designed to establish the non-inferior antiviral activity of a once daily DTG and ABC/3TC regimen compared to the once daily, current gold standard treatment regimen in this population: fixed dose combination (FDC) tablet of Atripla once daily.

The primary objective of Study ING114467 was to demonstrate the antiviral activity of GSK 1349572 plus ABC/3TC/FDC once daily therapy compared to Atripla over 48 weeks in HIV-1 infected ART-naïve subjects.

The secondary objectives were: 1) to demonstrate the antiviral activity of the GSK 1349572

plus ABC/3TC/FDC once daily therapy compared to Atripla over 96 weeks in HIV-1 infected ART-naïve subjects , and 2) to compare the tolerability, long term safety, and antiviral and immunologic activity of GSK 1349572 plus ABC/3TC FDC once daily therapy to Atripla over time.

Study ING112574/ VIKING-3

Study ING 112574 was designed to assess the antiviral activity and safety of DTG twice daily administered initially with a currently failing regimen but with an optional new background regimen after seven (7) days. The study population included highly active antiretroviral treatment (ART)-experienced HIV-1 infected adults who had experienced virological failure on an integrase inhibitor (INI) containing regimen associated with the emergence of INI resistant virus.

The primary objective of the study was to assess the antiviral activity of DTG 50 mg twice daily (BID) administered with failing background therapy to **Day 8** and thereafter with optimized background ART (OBR) consisting of at least one fully active agent through week 24 in HIV-infected adult subjects with virological failure on a prior INI containing regimen.

The secondary objectives were: 1) to assess the antiviral and immunologic activity of DTG over time, and 2) to characterize treatment emergent viral resistance in subjects experiencing virologic failure.

Study ING111762/ SAILING

Study ING 111762 was a 48 week phase III, randomized, double-blind, active-controlled, multicenter, parallel group, non-inferiority study. The study enrolled about 688 HIV-1 infected antiretroviral experienced, integrase-naïve subjects. Subjects were randomized in a 1:1 ratio to receive GSK 1349572 50 mg once daily or RAL 400 mg twice daily, each added to an investigator selected background regimen consisting of at least one fully active agent plus no more than one single agent which may or may not be active.

The primary objective of the study was to demonstrate the antiviral efficacy of GSK 1349572 50 mg once daily compared to RAL 400 mg BID both in combination with a background regimen consisting of one to two fully active single agents in HIV-1 infected, integrase inhibitor-naïve, therapy-experienced subjects at 48 weeks.

The secondary objectives were: 1) to demonstrate the antiviral efficacy of GSK 1349572 50 mg once daily compared to RAL 400 mg BID both in combination with a background regimen consisting of one to two fully active single agents in HIV-1 infected, integrase inhibitor-naïve ,therapy-experienced subjects at 24 weeks, 2) to assess the development of viral resistance in subjects experiencing virological failure, and 3) to explore exposure-response relationship between GSK 11349572 plasma exposure and virologic response or occurrence of adverse events over time.

The review division requested inspection of five clinical investigators for the pivotal protocols studies noted above because data from the protocols 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, and 2) the need to determine if sites conducted the trial ethically and were in compliance with GCP and local regulations.

The clinical sites of Hernandez-Mora (Spain), Lazzarin (Italy), and Lombard (South Africa) were chosen because of the enrollment of the largest number of subjects. The clinical sites of Pulido Ortega (Spain) and Hagins (US) were selected due to high enrollment and because no adverse events were observed in 41% and 40%, respectively, of the subjects enrolled at those sites

.II. RESULTS (by protocol/site):

Name of CI, location, and site #	**Protocol and # of subjects randomized**	**Inspection Dates**	**Final Classification**
Fedrico P. Ortega, M.D Avda Cordoba, s/n Madrid, Spain 28041 Site #083400	Protocol ING113086 Number of subjects: 23	April 15 to 19, 2013	Pending (preliminary classification NAI)
Adriano Lazzarin, M.D. Via Stamira d'ancona, 20 Milano Lombardia Italy 20127 Site# 089452	Protocol ING112574 Number of subjects: 17	April 22 to 25, 2013	Pending (preliminary classification NAI)
Miguel G.H-Mora, M.D. Avda Reyes Catolicos 2 Madrid Spain 28040 Site# 086910	Protocol ING114467 Number of subjects: 19	April 8 to 12, 2013	Pending (Preliminary classification NAI)
Johannes J. Lombard, M.D. 28 East Burger Street Bloemfontein South Africa 9301 Site #084854	Protocol ING111762 Number of subjects: 73	April 15 to 19, 2013	Pending (Preliminary classification NAI)
Debbie Hagins, M.D 107B FAHM Street Savannah, GA 31401 Site #081138	Protocol ING111762 Number of subjects: 26	April 15 to 19, 2013	Pending (Preliminary classification NAI)

Key to Classifications
NAI = No deviations
VAI = Deviation(s) from regulations
OAI = Significant deviations for regulations. Data unreliable.
Pending = Preliminary classification based on e-mail communication from the field; the Establishment Inspectional Report (EIR) has not been received from the field and complete review of EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

1. **Fredrico P. Ortega, M.D**
   Madrid, Spain 28041

   a. What Was Inspected: This inspection was performed as a data audit for NDA 204-790, Study Protocol ING 113086. At this site, a total of 27 subjects were screened, four subjects were reported as screen failures, 23 subjects were randomized into the study, 20 subjects completed the study, and 20 subjects continued into the extension phase of the study. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent prior to enrollment.

   The medical records/source data for 27 subjects were reviewed and compared to data listings. The review included consent forms, drug accountability records, inclusion/exclusion criteria, vital signs, IRB records, sponsor correspondence, and adverse events. Source documents for all subjects were compared to case report forms and data listings including for primary efficacy endpoints and adverse events listings.

   b. General Observations/Commentary: At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Ortega. The medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection. The study appears to have been conducted adequately, and the data generated may be used to support the pending application.

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

2. **Adriano Lazzarin, M.D.**
   Lombardia, Italy 20127

   a. What Was Inspected: This inspection was performed as a data audit for NDA 204790 Study Protocol ING112574. At this site, a total of 21 subjects were screened, and four subjects were reported as screen failures. Seventeen (17) subjects were randomized into the study, 14 completed the study, and 14 subjects continued on the extension phase of the study. Three subjects discontinued due to adverse events and the reason(s) were documented. Review of the Informed Consent Documents, for 21 subjects records reviewed, verified that all subjects signed consent forms prior to enrollment.

   The medical records/source documents for 21 subjects were reviewed for primary/secondary endpoints. The medical records/source documents for 21 subjects for certain visits were reviewed in depth, including drug accountability records, vital signs, IRB files, inclusion/exclusion criteria, prior and concomitant medications, and adverse events reporting. The field investigator compared the source documents/endpoint values to the data listings for primary efficacy endpoints, and no discrepancies were noted.

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

c. Assessment of Data Integrity: The data in support of the clinical efficacy and safety at Dr. Lazzarin's site are considered reliable and may be used in support of the pending application.

3. **Miguel G. Hernandez-Mora, M.D.**
   Madrid Spain 28040

a. What Was Inspected: This inspection was performed as a data audit for NDA 204-790 Study Protocol ING 114467. At this site, a total of 23 subjects were screened, four subjects were reported as screen failures, and 19 subjects were randomized into the study. A total of 16 subjects completed the study, and all 16 continued on to the extension phase of the study. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed consent forms prior to enrollment.

The medical records/source data for all subjects were reviewed including drug accountability records, vital signs, IRB records, prior and current medications, and inclusion/exclusion criteria. Source documents for all subjects were compared to data listings for primary efficacy endpoints and adverse events listing. There was no evidence of under-reporting of adverse events at this site. There were no known limitations to the inspection.

b. General Observations/Commentary: At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Mora. Our investigation found a minor protocol deviation, in that one subject was dispensed the wrong bottle of medication in error.

The medical records reviewed were verifiable based on the information available at the site. There were no known limitations to the inspection. There were no deaths and no evidence of under-reporting of adverse events.

c. Assessment of Data Integrity: Although a minor regulatory deviation was noted, the finding is unlikely to affect integrity of the data as they appear to be isolated incidence and not systemic in nature. The data from Dr. Mora's site are considered reliable and appear acceptable in support of the pending application.

4. **Johannes J. Lombard**
   Bloemfontein, South Africa 9301

a. What Was Inspected: This inspection was performed as a data audit for NDA 204-790, Study Protocol ING 111762. At this site, a total of 126 subjects were screened, 53 subjects were reported as screen failures, 73 subjects were randomized into the study,

and 53 subjects completed the study. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent prior to enrollment.

The medical records/source data for 15 subjects were reviewed and compared to data listings. The review included consent forms, drug accountability records, inclusion/exclusion criteria, vital signs, IRB records, sponsor correspondence, and adverse events. Source documents for all subjects were compared to case report forms and data listings including for primary efficacy endpoints and adverse events listings.

b. General Observations/Commentary: At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Lombard. The medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection. The study appears to have been conducted adequately, and the data generated may be used to support the pending application.

c. Assessment of Data Integrity: The data generated in support of the clinical efficacy and safety at Dr. Lombard's site is considered reliable and acceptable in support of the pending application.

5. **Debbie Hagins, M.D.**
   Savannah, GA 31401

a. What was Inspected: This inspection was performed as a data audit for NDA 204-790 Study Protocol ING111762. At this site, a total 34 subjects were screened, eight subjects were reported as screen failures, 26 subjects were randomized into the study, and 20 subjects completed the study. Review of the Informed Consent Documents for all subjects verified that all subjects signed consent forms prior to enrollment.

The medical records/source documents for all subjects were reviewed for primary/secondary endpoints. The medical records for the majority of subjects were reviewed in depth, including drug accountability records, vital signs, IRB files, inclusion/exclusion criteria, study procedures, monitoring procedures, and use of concomitant medications. Source documents were compared to CRFs and data listings, to include primary efficacy endpoints and adverse events.

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

c. Assessment of Data Integrity: The data generated in support of the clinical efficacy and safety at Dr. Hagins's site is considered reliable and acceptable in support of the pending application.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Five clinical investigator sites were inspected in support of this application. The inspection of the five clinical investigators listed above revealed no regulatory violations, and the pending classification for these inspections is No Action Indicated (NAI). An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR. Overall, the data submitted from these five sites are considered acceptable in support of the pending application.

{See appended electronic signature page}

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

CONCURRENCE:

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Susan Leibenhaut, M.D.
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANTOINE N EL HAGE
05/14/2013

SUSAN LEIBENHAUT
05/14/2013

SUSAN D THOMPSON
05/14/2013

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

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

Application: NDA 204790

Application Type: New NDA

Name of Drug: (dolutegravir, GSK1349572) tablet, 50mg

Applicant: ViiV Healthcare

Submission Date: December 16, 2012

Receipt Date: December 17, 2012

Regulatory History and Applicant's Main Proposals
On December 17, 2012 Viiv submitted this original NDA for dolutegravir tablets for the treatment of HIV infection. This is an NME NDA filed under "The Program" of PDUFA V. A Pre-NDA meeting was held on September 20, 2012 to discuss the content and format of this NDA.

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

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

In addition, the following labeling issues were identified:

1. Pregnancy registry information should not be in USE IN SPECIFIC POPUALITONS section of Highlights.
2. The revised date should only be at the end of the highlights section of the PI.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by March 15, 2013. The resubmitted PI will be used for further labeling review.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

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

Highlights (HL)

GENERAL FORMAT

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

Comment:

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment:

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is

the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES 6. Section headings are presented in the following order in HL:

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

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

Comment:

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

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

Comment:

Product Title

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

Comment:

Initial U.S. Approval

YES

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

Comment:

Boxed Warning

N/A 12. All text must be **bolded**.

Comment:

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

Comment:

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

Comment:

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

Comment:

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

Comment:

Recent Major Changes (RMC)

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

Comment:

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

Comment:

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

Comment:

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

Comment:

Indications and Usage

YES

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

Comment:

Dosage Forms and Strengths

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

Comment:

Contraindications

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

Comment:

N/A 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

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

Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

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

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

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

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

Comment:

Revision Date

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

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

NO 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

Subsection 8.1 to 8.5 should ordered:

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

YES 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

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

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

Comment:

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

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

Comment:

Patient Counseling Information

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

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

Comment:

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

/s/

SOHAIL MOSADDEGH
02/28/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 204790 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Tivicay (proposed) Established/Proper Name: Dolutegravir, GSK1349572 Dosage Form: tablet Strengths: 50 mg		
Applicant: ViiV Healthcare Company Agent for Applicant (if applicable): GlaxoSmithKline		
Date of Application: 12/17/2012 Date of Receipt: 12/17/2013 Date clock started after UN:		
PDUFA Goal Date: 08/17/2013	Action Goal Date (if different): 08/16/2013	
Filing Date: 02/15/2013	Date of Filing Meeting: 01/25/2013	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 1		
Proposed indication(s)/Proposed change(s): in combination with other antiretroviral agents for the treatment of HIV infection in adults and pediatric patients aged 12 years and older		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted

Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐

Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☒ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 101429, 063468, 75382, 110847	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [**see 21 CFR 314.54(b)(1)].**				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [**see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above 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***				
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:				

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***		X		

Designations and Approvals list at: ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***				

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

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

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

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Applications in "the Program" (PDUFA V) (NME NDAs/Original BLAs)	**YES**	**NO**	**NA**	**Comment**
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?	**X**			method validation report for telaprevir
• If yes, were all of them submitted on time?	**X**			01/16/13
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	**X**			
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	**X**			
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), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			originally signed by GSK. Resubmitted 01/29/13 signed by Viiv

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

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff :*			**X**	

Pediatrics	**YES**	**NO**	**NA**	**Comment**

PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	X			Submitted addendum to summarize pediatric plan on 01/29/13
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	X			submitted 01/29/13
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		partially addresses the WR (with the adolescent data), but the trials are ongoing
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X			
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labels			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

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

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

All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		X		
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 02/11/2001 ***If yes, distribute minutes before filing meeting***	X			07/26/2010 CMC EOP2
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 09/20/2012 ***If yes, distribute minutes before filing meeting***	X			07/10/2012 CMC pre-NDA
Any Special Protocol Assessments (SPAs)? **Date(s):** 12/22/2009 & 12/23/2009 ***If yes, distribute letter and/or relevant minutes before filing meeting***	X			

ATTACHMENT

MEMO OF FILING MEETING

DATE: 01/25/2013

NDA: 204790

PROPRIETARY NAME: Tivicay (proposed)

ESTABLISHED/PROPER NAME: dolutegravir

DOSAGE FORM/STRENGTH: 50 mg tablets

APPLICANT: ViiV Healthcare Company

PROPOSED INDICATION: in combination with other antiretroviral agents for the treatment of HIV infection in adults and pediatric patients aged 12 years and older

BACKGROUND: GlaxoSmithKline LLC submitted NDA 204790 for TIVICAY (dolutegravir) tablets on behalf of ViiV Healthcare on 12/17/2012. This was submitted as an NME NDA under the PDUFA V review program ("The Program"). Dolutegravir is an orally administered integrase inhibitor being developed for the treatment of HIV infection. The clinical studies supporting this program were conducted under IND 075382: ING113086 (SPRING-2), ING114467 (SINGLE), ING112574 (VIKING-3) and ING111762 (SAILING). At the 09/20/2012 Pre-NDA meeting, agreement was made on the contents of the NDA with agreement reached that the method validation report for telaprevir could be submitted within 30 days of the NDA submission.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Sohail Mosaddegh	Y
	CPMS/TL:	Karen Winestock Katherine Schumann (Acting)	Y
Cross-Discipline Team Leader (CDTL)	Kim Struble		Y
Clinical	Reviewer:	Charu Mullick Wendy Carter Yodit Belew	Y/Y/Y
	TL:	Kim Struble	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		

OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	Lisa Naeger	N
	TL:	Julian O'Rear	Y

Clinical Pharmacology	Reviewer:	Su-Young Choi Stanley Au	Y/Y
	TL:	Shirley Seo	Y
Biostatistics	Reviewer:	Thomas Hammerstrom	Y
	TL:	Guoxing (Greg) Soon	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Mark Seaton	Y
	TL:	Hanan Ghantous	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Lin Qi Maotang Zhou	Y/Y
	TL:	Steve Miller	Y
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Ghosh Krishna	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	TBD	
	TL:	Jamie Wilkins Parker	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Biopharmaceutics Reviewer	Deepika Lakhani TL: Angelica Dorantes		N/Y
Patient Labeling Reviewer	Latonia Ford TL: Barbara Fuller		N/N
DDMAC – Consumer Reviewer	Asante Oluwaseun		Y
DDMAC – Professional Reviewer	Jessica Fox		Y
Edward M Cox, MD, MPH, Director, Office of Antimicrobial Products Jeffrey Murray, MD, MPH, Deputy Director Jeffry Florian, PhD, Pharmacometrics Reviewer Karen Winestock, Chief, Project Management Staff, DAVP Katherine Schumann, MS, Acting CPMS Kendall Marcus, MD, Associate Director of Safety Sohail Mosaddegh, PharmD, Regulatory Project Manager Danyal Chaudhry, OSE RPM Jenny Zheng, PhD, Clinical Pharmacology Reviewer			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments	☐ Not Applicable

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

Comments:	☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Office level

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): 03/13/2013

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

Comments:

12. Communicate Filing Review Issues (3.2.2)	03/01/13
13. Communicate "Program" Review Timeline to Applicant (3.3) (if applicable)	03/01/13
Milestones for Step Four: Conduct Review	
14. Conduct Review (4)	Month 1.0-5.0
15. If applicable, discuss safety findings with OSE (re: REMS, PMRs) and OC-OSI (re: REMS)	03/13/13
16. Hold Mid-Cycle Meeting (4.4)	03/13/13
17. Post-Mid-Cycle Meeting Communication with Applicant (4.5)	03/27/13
18. Complete Primary Reviews, including Secondary Review Sign-Off (4.9)	05/17/13
19. Complete Secondary Review (when needed) (4.9)	05/20/13
20. Issue Discipline Review Letters (4.10)	05/20/13
21. Hold Wrap-Up Meeting, including Safety Discussion (4.16)	06/28/13
22. Complete CDTL Memo (4.17)	07/19/13
Milestones for Labeling, PMRs/PMCs, REMS	
23. If indicated, send REMS Notification Letter (REMS memo must be completed) (4.5)	04/24/13
24. Begin REMS Discussions with Applicant (if not already started) (4.8.2)	06/17/13
25. Review Team Drafts Labeling, PMC, PMR (4.8.1)	05/03/13
26. Send Labeling/PMR/PMC to Applicant (4.8.1)	05/17/13
27. Labeling/PMR/PMC Discussions with Applicant Begin (4.8.1)	05/24/13
Milestones for Late-Cycle Meeting with no AC meeting	
28. Hold Pre-Meeting for Late-Cycle Meeting (4.12)	05/17/13
29. Send Agency Late-Cycle Meeting Briefing Package to Applicant (4.13)	05/30/13
30. Hold Late-Cycle Meeting with Applicant (4.13)	06/11/13
Milestones for Step 5: Take Action	
39. Hold PeRC meeting	07/10/13
40. Compile and Circulate Action Letter and Action Package (5.2)	07/26/13
41. Division Director Review of Action Package and Decision - memo in DARRTS	08/07/13
42. REMS finalized; DRISK review of REMS finalized (5.2)	07/12/13
43. ODE Review of Action Package and Decision (5.1) -memo in DARRTS	08/14/13
45. Issue Action Letter (5.2)	08/16/13

REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☐ Standard Review ☒ Priority Review
ACTIONS ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into track system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to c EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☒	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for NME NDAs in "the Program")
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These s may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Appendix A (NDA and NDA Supplements only)

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

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

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

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

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

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

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

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

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

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

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

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/s/

SOHAIL MOSADDEGH
02/13/2013