CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213983Orig1s000

OTHER REVIEW(S)

Division of Antiviral Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 204790/S-25
NDA 213983

Name of Drug: Tivicay (dolutegravir) tablet, 10 mg, 25 mg, and 50 mg
Tivicay PD (dolutegravir) tablet for oral suspension, 5 mg

Applicant: ViiV Healthcare Company

Labeling Reviewed

Submission Date and Receipt Date: June 11, 2020

Reviewed Items: The proposed labeling submitted by the applicant on June 11, 2020, was compared to the last approved labeling dated October 24, 2019 (NDA 204790/S-24).

Background: Tivicay and Tivicay PD are HIV-1 integrase strand transfer inhibitors indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection.

On December 12, 2019, ViiV Healthcare Company, submitted a prior approval supplement (efficacy) and an original NDA application:

NDA 204790/S-25

- To expand the patient population to include patients weighing 14 kg to less than 30 kg
- To revise the dosing recommendations for patients weighing 30 kg to less than 40 kg

NDA 213983

- To provide a new dosage form, tablet for oral suspension, for patients weighing at least 3 kg

Key changes made within the USPI will be outlined in this review. For more detailed information, reference the attached labeling and discipline reviews.

Review

General

- Minor editorial changes were made throughout the label (i.e. spacing, grammar and capitalization)
- Addition of Tivicay PD and dolutegravir where applicable throughout labeling

Highlights of Prescribing Information

- Tivicay PD was added as the tradename for the new formulation of dolutegravir, tablets for oral suspension
- Under RECENT AND MAJOR CHANGES, Indications and Usage, Dosage and Administration, and Warnings and Precautions, Different Formulations Are Not Interchangeable were added along with the 06/2020 date
- INDICATIONS AND USAGE
    - Amended the indication statement to add pediatric patients at least 4 weeks of age and weighing 3 kg for Tivicay and Tivicay PD
    - Updated second indication statement to specify use of Tivicay with rilpivirine.
- DOSAGE AND ADMINISTRATION
    - Updated to added Tivicay PD dosing recommendations for pediatric patients at least 4 weeks and weighing 3 kg.
    - Addition of alternative dosing recommendations for Tivicay tablets for patients weighing at least 14 kg
- DOSAGE FORMS AND STRENGTHS
    - Addition of Tivicay PD tablets for oral suspension
- Under WARNINGS AND PRECAUTIONS, an additional section was added to state that Tivicay and Tivicay PD are not interchangeable
- The date was revised to reflect the present approval month and year

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Full Prescribing Information: Contents*

- Revisions to the Table of Contents to reflect updates made in labeling
    - 2 DOSAGE AND ADMINISTRATION previous subsections revisions and new subsections added:
        - Revision
            - 2.1 Pregnancy Testing before Initiation
            - 2.2 Recommended Dosage in Adults
            - 2.3 General Dosing and Administration Instructions for Pediatric Patients
        - New Subsection
            - 2.4 Recommended Dosage in Pediatric Patients Weighing 3 to 14 kg
            - 2.5 Recommended Dosage in Pediatrics Patients Weighing 14 kg or Greater
            - 2.6 Additional Administration Instructions
    - 5 WARNINGS AND PRECAUTIONS
        - Addition of new subsection, 5.6 Different Formulations Are Not Interchangeable

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US Prescribing Information

The following substantive changes were made to the Full Prescribing Information of the labeling:

1 INDICATION AND USAGE

- Addition of pediatric patients at least 4 weeks and weighing at least 3 kg to the first indication sentence
- Specify Tivicay indication when used in combination with rilpivirine as a complete regimen

2 DOSAGE AND ADMINISTRATION

- Revision previous subsections and addition of new subsections
    - 2.3 Revised to state General Dosing and Administration Instructions for Pediatric Patients
        - New information on use of Tivicay and Tivicay PD and lack of interchangeability
    - 2.4 Recommended Dosage in Pediatric Patients Weighing 3 to 14 kg
        - New subjection added with dosing recommendations for patients at least 4 weeks old and 3 kg to 14 kg.
    - 2.5 Recommended Dosage in Patients Weighing 14 kg or Greater
        - Added Tivicay PD dosing recommendations for patients 14 kg or greater.
        - Provided new or revised Tivicay dosing recommendations for pediatric patients weighing 14 kg or greater
    - 2.6 Additional Administrative Instructions
        - New information on the administration of Tivicay and Tivicay PD with or without food

3 DOSAGE FORMS AND STRENGTHS

- Added information on Tivicay PD tablets for oral suspension

5 WARNINGS AND PRECAUTIONS

- Addition of new subsection, 5.6 Different Formulations Are Not Interchangeable

6 ADVERSE REACTIONS

- Updates to 6.1 Clinical Trials Experience, Clinical Trials Experience in Pediatric Subjects with information on safety and pharmacokinetics of Tivicay and Tivicay PD in pediatric patients 4 weeks and older and weighing at least 3 kg

7 DRUG INTERACTIONS

- Added potassium channel blocker dalfampridine to (b) (4) Table 8 Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May

Be Recommended Based on Drug Interaction Trials or Predicted Interactions *[see Dosage and Administration (2)]*

8 USE IN SPECIFIC POPULATIONS

- Updates to 8.4 Pediatric Use were made to include safety and pharmacokinetic information on Tivicay and Tivicay PD in pediatric subjects aged 4 weeks and older and weighing at least 3 kg
- Revised statement under 8.7 Renal Impairment to state there is inadequate information to recommend dosing of dolutegravir in patients requiring dialysis

11 DESCRIPTION

- Added Tivicay PD tablet for oral suspension drug product information

12 CLINICAL PHARMACOLOGY

- 12.3 Pharmacokinetics
    - Updated with information on the two dosage forms, Tivicay tablets and Tivicay PD tablets for oral suspension not being bioequivalent and not interchangeable.
    - New information added on the pharmacokinetics of dolutegravir in pediatric patients under Specific Populations
    - Updated Table 10 Summary of Pharmacokinetic Parameters in Pediatric HIV-1 Infected Subjects (Pool Analyses for IMPAACT P1093 and ODYSSEY Trials) with new pediatric weigh bands, dose of Tivicay PD, number of subjects, and PK parameter geometric means.
    - Updating Patients with *Renal Impairment* with trial information and dosing recommendations.

14 CLINICAL STUDIES

- 14.1 Description of Clinical Studies was updated to include pediatric information from IMPAACT P1093 trial and new dosage form Tivicay PD
- 14.3 Pediatric Subjects
    - Addition of clinical information from IMPAACT P1093, Cohort 3 (2 to less than 6 years), Cohort 4 (6 months to less than 2 years) and Cohort 5 (4 weeks to less than 6 months)

16 HOW SUPPLIED/STORAGE AND HANDLING

- Addition of Tivicay PD description, packaging, and storage conditions information.

17 PATIENT COUNSELING INFORMATION

- Added Instructions for Use to the FDA advice for patients' sentence.
- Addition of Different Formulations since Tivicay and Tivicay are not bioequivalent and are not interchangeable

- Addition of Administration Instructions to avoid dosing errors and ensure patients and caregivers that Tivicay PD may be swallowed whole or dispersed in drinking water.
- Update storage conditions with Tivicay PD information

Patient Information

What is Tivicay or Tivicay PD?

- Added information on Tivicay PD and use in patients at least 4 weeks and weighing at least 3kg.

Before you take Tivicay or Tivicay PD, tell your healthcare provider about all of your medical conditions, including if you:

- Removed "have ever had an allergic reaction to dolutegravir" from this section

How should I take Tivicay or Tivicay PD?

- Added information on how to prepare Tivicay PD for children who are unable to swallow.
- Added a statement about Tivicay PD not being the same as Tivicay and cannot be substituted for each other.

How should I store Tivicay or Tivicay PD?

- Information on storage conditions for Tivicay PD was added

What are the ingredients in Tivicay and Tivicay PD?

- Inactive ingredients in Tivicay PD was added.

Patient Information Date

- Revised date changed to "06/2020"

Instruction for Use

- Added new section of labeling to provide instruction on how to prepare Tivicay PD oral suspension

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Recommendations

Based upon the changes highlighted in this review and the reviews from the clinical pharmacology and clinical disciplines, this supplement should be approved. Please see the individual reviews for additional information.

Linda C. Akunne

Regulatory Project Manager Date

Karen Winestock

Chief, Project Management Staff Date

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LINDA C AKUNNE
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 10, 2020
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 213983 and NDA 204790/S-025
Product Name and Strength:	Tivicay PD (dolutegravir) tablets for oral suspension, 5 mg
Applicant/Sponsor Name:	ViiV Healthcare Company (ViiV)
OSE RCM #:	2019-2562, 2019-2561, 2019-2586-1
DMEPA Safety Evaluator:	James Schlick, MBA, RPh
DMEPA Team Leader:	Millie Shah, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on June 3, 2020 for Tivicay PD. The Division of Antivirals (DAV) requested that we review the revised container label and carton labeling for Tivicay PD (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Schlick J. Human Factors Results and Label and Labeling Review for Tivicay PD (NDA 213983 and NDA 204790/S-025). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 May 15. RCM No.: 2019-2562;2019-2561;2019-2586.

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

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

Memorandum

Date: May 22, 2020

To: Linda Akunne, Regulatory Project Manager
Division of Antiviral Products (DAVP)

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

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for TIVICAY (dolutegravir) tablets, for oral use and TIVICAY PD (dolutegravir) tablets for oral suspension

NDA: 204790/S-025 &
213983

In response to DAVP consult request dated December 26, 2019, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and Instructions for Use (IFU), and Carton and Container labeling for the original NDA submission for NDA 213983 TIVICAY PD (dolutegravir) tablets for oral suspension (TIVICAY PD), and a Prior Approval Supplement for NDA 204790/S-025 TIVICAY (dolutegravir) tablets, for oral use (TIVICAY). This supplement and original NDA proposes a new dosage form and new and revised dosing recommendations for patients weighing 14 to < 30 kg.

PI and PPI/IFU: OPDP's comments on the proposed labeling are based on the draft PI and PPI/IFU received by electronic mail from DAVP (Linda Akunne) on May 15, 2020, and comments on the PI are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI/IFU were sent under separate cover on May 21, 2020.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling emailed by the Sponsor to DAVP (Linda Akunne) on May 22, 2020, and we do not have any comments.

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

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

PATIENT LABELING REVIEW

Date:	May 21, 2020
To:	Linda Akunne **Division of Antivirals (DAV)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA, CPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Wendy Lubarsky, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name), Dosage Form, Route, Application Type/Number, and Supplement Number:	TIVICAY (dolutegravir), tablets, for oral use, NDA 204790/S-025 TIVICAY PD (dolutegravir), tablets, for oral suspension, NDA 213983
Applicant:	ViiV Healthcare Company

1 INTRODUCTION

On December 12, 2019, ViiV Healthcare Company submitted for the Agency's review a Prior Approval Supplement (PAS) to their New Drug Application (NDA) 204790/S-025 for TIVICAY (dolutegravir), tablets, for oral use and an original NDA 213983 for (b) (4) (dolutegravir), tablets, for oral (b) (4). This supplement and original NDA proposes a new dosage form and new and revised dosing recommendations for patients weighing 14 to < 30 kg.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antivirals (DAV) on December 26, 2019 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for TIVICAY (dolutegravir), tablets, for oral use and (b) (4) (dolutegravir), tablets, for oral (b) (4).

2 MATERIAL REVIEWED

- Draft TIVICAY (dolutegravir), tablets, for oral use and (b) (4) (dolutegravir), tablets, for oral (b) (4) PPI and IFU received on December 12, 2019, and received by DMPP and OPDP on May 15, 2020.
- Draft TIVICAY (dolutegravir), tablets, for oral use and (b) (4) (dolutegravir), tablets, for oral (b) (4) Prescribing Information (PI) received on December 12, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 15, 2020.

3 REVIEW METHODS

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

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.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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LABEL AND LABELING AND HUMAN FACTORS RESULTS REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	May 15, 2020
Requesting Office or Division:	Division of Antivirals
Application Type and Number:	NDA 213983 and NDA 204790/S-025
Product Name, Dosage Form, and Strength:	(b) (4) (dolutegravir) tablets for oral suspension, 5 mg Tivicay (dolutegravir) tablets, 10 mg, 25 mg, and 50 mg
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	ViiV Healthcare Company (ViiV)
FDA Received Date:	December 12, 2019; February 19, 2020; April 3, 2020; April 24, 2020
OSE RCM #:	2019-2562, 2019-2561, 2019-2586
DMEPA Safety Evaluator:	James Schlick, MBA, RPh
DMEPA Team Leader:	Millie Shah, PharmD, BCPS
Associate Director for Human Factors:	QuynhNhu Nguyen, MS

1 REASON FOR REVIEW

We reviewed the human factors (HF) validation study report and proposed labels and labeling submitted under NDA 213983 for [redacted] (b) (4) (dolutegravir) tablets for oral suspension. The applicant is proposing tablets for oral suspension co-packaged with a 30-mL dose measuring cup and 10-mL oral dosing syringe for patients aged at least 4 weeks and weighing at least 3 kg. We also reviewed the proposed revisions to the Prescribing Information under NDA 204790/S-025, which was submitted concurrently with NDA 213983,to update the Tivicay label with revised dosing recommendations for patients weighing 30 kg to less than 40 kg and with new dosing recommendations for the expanded pediatric population for patients weighing 14 kg to less than 30 kg.

2 REGULATORY HISTORY

We previously reviewed the human factors (HF) protocol and clarifying questions from the Sponsor submitted under IND 075382 and provided comments to the Sponsor.[a,b,c,d] The Sponsor incorporated all our recommendations, except the Patient Labeling Team (PLT) comments for the Instructions for Use (IFU) sent in the April 4, 2019 letter to the Sponsor as they had already begun their HF validation study. The Sponsor incorporated PLT's comments after the HF study was conducted. See Section 4 for further discussion.

3 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Validation Study	C
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Information Request	F

[a] Wilson, V. Human Factors Protocol Review for dolutegravir tablets for oral suspension (IND 075382). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018-NOV-19. RCM No.: 2018-1991.

[b] Wilson, V. Human Factors Protocol Review Memorandum for dolutegravir tablets for oral suspension (IND 075382).Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018-DEC-11. RCM No.: 2018-1991-1.

[c] Wilson, V. Human Factors Protocol Review Memorandum for dolutegravir tablets for oral suspension (IND 075382). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019-MAR-18. RCM No.: 2018-1991-2.

[d] Schlick J. Human Factors Protocol Review for dolutegravir tablets for oral suspension (IND 075382). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019-MAY 8. RCM No.: 2019-1991-3.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

HF Results and Instructions for Use

The sections below provide a summary of the HF study design, errors/close calls/use difficulties observed with critical and essential tasks (Table 3 and Section 4.3), and our analysis to determine if the HF study results support the safe and effective use of the proposed product.

The Sponsor indicated in their HF validation study report that they intend to revise the IFU after conducting the HF validation study (Section 12.1, See Appendix C for a link to the HF results report document). We asked the Sponsor to indicate if they submitted their intend-to-market IFU and if the revisions were incorporated in the intend-to-market IFU. The Sponsor replied that they submitted the intend-to-market IFU with revisions and provided an explanation for the rationale of the revisions. The revisions made to the IFU involved non-critical tasks and, therefore, we determined that new risks to critical tasks were not introduced and do not require conducting another HF validation study. See Appendix F for more information.

4.1 SUMMARY OF STUDY DESIGN

Table 2 presents a summary of the HF validation study design. See Appendix C for more details on the study design.

Table 2. Study Methodology for Human Factors (HF) Validation Study	
Study Design Elements	Details
Participants	User Group 1: Parents of children ages 4 weeks to 12 years of age (n=15) User Group 2: Grandparents or other adult caregivers of children ages 4 weeks to 12 years of age (n=15)
Training	No training was provided to participants. Participants were not coached or guided in any way. The product and IFU were made available to participants to use as they normally would.
Test Environment	Simulated home setting
Dosing Scenario	Scenario 1: A low dose scenario (i.e. 1, 2, or 3 tablets)

	Scenario 2: A high dose scenario (i.e. 4, 5, or 6 tablets)
Sequence of Study	Part 1: Simulated use of Scenario 1 and then Scenario 2 Part 2: Knowledge Task Question or Comprehension Interview Part 3: Post-Use Interview to assess root causes for any use errors, close calls, or difficulties

4.2 RESULTS AND ANALYSES

TABLE 3: SUMMARY AND ANALYSES OF ERRORS/CLOSE CALLS/USE DIFFICULTIES OBSERVED WITH CRITICAL TASKS					
Tasks	Number of Failures/Use Errors, Close Calls and Use Difficulties	Description of Failures/Use Errors, Close Calls and Use Difficulties	Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Task 2 "Place correct number of tabs in the dosing cup	1 use error	There was 1 error for this task (Participant 02-014). This participant misinterpreted the dosing scenario. When probed by the Interviewer, he explained that he assumed the scenario was communicating 3 doses of 1 tablet throughout the day (i.e. 1 tab tid), though the scenario stated a dose of 3 tablets. Therefore, he only used 1 tablet. From Appendix 15.6 *Mary is your 3-year-old daughter. She is a lively*	The root cause of the error was misunderstanding of the scenario.	The Sponsor considered this to be an artifact of the test and no additional mitigation strategies were discussed.	We agree the root cause of this error was a misunderstanding of the scenario (i.e., test artifact). We have no recommendations at this time.

TABLE 3: SUMMARY AND ANALYSES OF ERRORS/CLOSE CALLS/USE DIFFICULTIES OBSERVED WITH CRITICAL TASKS					
Tasks	Number of Failures/Use Errors, Close Calls and Use Difficulties	Description of Failures/Use Errors, Close Calls and Use Difficulties	Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
		child who eats well but is reluctant to drink. She has been prescribed this medicine. Her dose is 3 tablets every day. Please prepare a dose for Mary and simulate the administration of her dose.			
Task 4 Administer the full dose	2 use errors 1 use difficulty	Use error: 02-007 poured 15 mL of water in to the cup, but only drew up 5 mL in the syringe to deliver the dose. Use error: 01-016 poured 10 mL into the cup instead of 5 mL. He stopped when he realized his mistake and did not continue.	02-007 – Did not read the instructions fully and relied on the instructions to draw up 5 mL. 01-016 thought he put too much water in the cup and should stop the simulation and not continue.	02-007 – No additional mitigation strategies were discussed. 01-016 – The Sponsor considered this to be an artifact of the	We note that participant 02-007 correctly prepared and administered the second dose in scenario 2. Both scenario 1 and scenario 2 did not include training. We also reviewed the IFU and it states to "draw up all the medicine into the syringe by pulling up on the plunger"

TABLE 3: SUMMARY AND ANALYSES OF ERRORS/CLOSE CALLS/USE DIFFICULTIES OBSERVED WITH CRITICAL TASKS					
Tasks	Number of Failures/Use Errors, Close Calls and Use Difficulties	Description of Failures/Use Errors, Close Calls and Use Difficulties	Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
		Use difficulty: 01-003 – Struggled to bring up amount of dose leftover after initial draw into syringe, but ultimately delivered the full dose.	01-003 – The difficulty was due to the angle at which the participant held the dosing cup and the syringe, making it difficult to extract the entire dose.	test and no additional mitigation strategies were discussed. 01-003 - No additional mitigation strategies were discussed.	For 01-016 we agree the error was due to an artifact of the test and no additional mitigation strategies are necessary. Additionally, this recorded error is a result of an error that occurred in a previous step. For 01-003 we note that the participant correctly prepared and administered the second dose in scenario 2. Both scenario 1 and scenario 2 did not include training. This participant's correct administration in scenario 2 may be due to improved technique as the participant improved their

TABLE 3: SUMMARY AND ANALYSES OF ERRORS/CLOSE CALLS/USE DIFFICULTIES OBSERVED WITH CRITICAL TASKS					
Tasks	Number of Failures/Use Errors, Close Calls and Use Difficulties	Description of Failures/Use Errors, Close Calls and Use Difficulties	Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
					handling of the devices to prepare and administer the dose. Thus, we find the residual risk acceptable for these errors, and we have no recommendations at this time.
Comprehension Question 8A. "Dawn prepares the medicine and gives it to her son using the dosing cup according to the instructions." "Her son swallows the	8 participants did not answer the question correctly	Incorrect responses include the following: 7 participants -"Clean/wash out dosing items and cup" 1 participant – "Make sure there is no more medicine left"	3 participants failed to mention the importance of the rinse step in their response 3 participants misunderstood the question scenario. These participants thought that the adult should clean the cup as the very next step and	The Sponsor indicated that the root cause was likely due to participants not understanding that the question was meant to test the importance of the rinse	We agree with the Sponsor's assessment of the mitigation strategies. Thus, we find the residual risk acceptable for these errors, and we have no recommendations at this time.

TABLE 3: SUMMARY AND ANALYSES OF ERRORS/CLOSE CALLS/USE DIFFICULTIES OBSERVED WITH CRITICAL TASKS					
Tasks	Number of Failures/Use Errors, Close Calls and Use Difficulties	Description of Failures/Use Errors, Close Calls and Use Difficulties	Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
medicine from the dosing cup and hands the cup back to his mother." "According to the instructions, what is the very next step Dawn should take?"		The Sponsor included the rationale for the question: All the medicine must be given to the child. The initial swirl step should fully disperse the tablet(s) for administration, but if small amounts remain, they should add more water, swirl and give to the child.	assumed swirling an additional 5 mL of water in the dosing cup and giving it to the child (the correct answer) had already been done. 2 participants did not read the instructions fully on the IFU.	step. The user tasks in the simulated use portion of the study indicate that users understand the need to check and assess if a small amount remains a rinse step should be done to administer the full dose.	

4.3 ANALYSIS OF ESSENTIAL/NON-CRITICAL TASKS

We acknowledge that there were use-related issues (e.g. use errors, close calls, or use difficulties) on non-critical tasks (e.g. pour an approximate amount of additional water into the dosing cup and administer the rinse dose) submitted in the HF study results report. However, our review of the subjective feedback and root cause analyses did not generate any concerns from a medication error perspective, and we find the risks are mitigated to an acceptable level. Thus, we did not include these non-critical tasks within this review.

4.4 LABELS AND LABELING

We identified concerns with the label and labeling from a medication error perspective. See the table in Section 5.1 for the Division and the table in Section 5.2 for the Applicant that include the identified medication error issues with the submitted label and labeling, our rationale for concern, and the proposed recommendation. At this time, we have determined that these recommendations do not require additional human factors validation study data to be submitted for review.

30-Count Bottle

We identified a medication error concern with the 60-count tablet bottle. The Prescribing Information indicates that the tablets for oral suspension should be dispensed in the original container. We are concerned that pharmacists, due to insurance coverage issues, may dispense some tablets in a pharmacy vial to meet the quantity specified on a prescription. For example, a pediatric patient that is prescribed 3 tablets per day would need 90 tablets for a 30 day supply. If the prescriber writes for a quantity of 90 tablets and insurance coverage requires a 30 day supply, then the pharmacist would need to dispense 60 tablets in the original container and 30 tablets in an amber pharmacy vial to meet the requirement. This could possibly lead to drug degradation, resulting in an underdose. We sent an information request (IR) on March 27, 2020 to seek the Sponsor's plan to mitigate this risk. The Sponsor provided their rationale in a response dated April 3, 2020 (See Appendix F).

We note the Sponsor's assessment that as children grow and progress through the weight bands new prescriptions written in between the end of a 30 day supply may not offset the possibility of a partial dose remaining at the end of a 30-fill count bottle's use. We agree with their assessment that a 30-count bottle will not solve all scenarios. Additionally, we expect that prescribing patterns will adapt to correct quantity dispensed after the product is on the market. ViiV noted in their April 3, 2020 IR response that a (b) (4) is being developed (b) (4) . Moreover, we provide additional comments to increase the prominence of the storage statement to dispense in the original container. Thus, given the totality of information we believe these strategies should provide appropriate risk mitigations for this medication error concern.

25 mg film-coated tablet strength

We note that the 25 mg strength is still listed in Section 16, How Supplied/Storage and Handling. However, with the proposed dosing in Section 2, Dosage and Administration, the doses prescribed for the film-coated tablet do not require the need for a 25 mg tablet. We are concerned because the oral tablets for suspension and film-coated tablets are not interchangeable. If the 25 mg regular tablet is still on the market, there could be confusion between the oral tablet for suspension dose of 25 mg and the 25 mg strength of the film-coated tablet. The pharmacokinetic differences between the dosage forms could lead to an overdose or underdose depending on the result of the medication error.

We sent an IR on March 27, 2020 to the Sponsor asking about the marketing status of the 25 mg tablet. The proposed dosing does not include the need for a 25 mg film coated tablet, but information on the tablet is included in Section 16 "How Supplied/Storage and Handling" of the PI. The Sponsor responded on April 3, 2020 and indicated that they have no immediate plan to withdraw the 25 mg film-coated tablet because the Sponsor intends to provide adult patients a choice on how they take their 50 mg dose (2 x 25 mg tablets or 1 x 50 mg tablet). We provide a recommendation in Section 5.1 to the division to consider the option of 2 x 25 mg film-coated tablets to achieve a 50 mg dose in the dosing table in Section 2, Dosage and Administration, of the PI.

The medication error concern of product selection between non-bioequivalent products and the inclusion of a modifier, "PD", to the proprietary name to mitigate this risk will be addressed under a separate proprietary name review cover. From a label and labeling perspective, we provide a comment in Section 5.2 to address this risk.

10 mg film-coated tablet strength

We note that the Sponsor has proposed a dose for children weighing 14-20 kg using the film coated tablet at a dose of 40 mg (4 x 10 mg). This represents a considerable pill burden for small children and a choking hazard (b) (4) (b) (4) The medication error concern of product selection between non-bioequivalent products and the inclusion of a modifier, "PD", to the proprietary name to mitigate this risk will be addressed under a separate proprietary name review cover.

Proposed Dosing Table in Section 2.3 Pediatric Patients

We note that in patients weighing (b) (4), the dosing table gives (b) (4) to achieve the dose based on weight. In an internal meeting during the review cycle, the medical officer for this product conveyed his concern that the table is confusing given the option of (b) (4) See the image below to further illustrate the confusion. We agree with this assessment and provide a recommendation in Section 5.1 to address the risk for this medication error concern.

(b) (4)

5 CONCLUSION

The results of the HF validation study identified failures, close calls, and use difficulties with critical and essential tasks. Our evaluation of the proposed label and labeling identified areas of vulnerability that may lead to medication errors. In Section 5.1 (Division) and Section 5.2 (Applicant), we have provided recommendations and we recommend that the revisions be implemented prior to the approval of the NDA. In this particular instance, we have determined that that these changes can be implemented without additional validation testing to be submitted for review.

5.1 RECOMMENDATIONS FOR THE DIVISION

Identified Issues and Recommendations for Division of Antivirals			
	Identified Issue	Rationale for Concern	Recommendation
Highlights of Prescribing Information			
1.	Pediatric doses using the film coated tablet are not included in Section 2, Dosage and Administration	This option should be presented to inform prescribers	Consider including a separate table that includes dosing using the film coated tablet for pediatric patients
2.	The statement that the tablet for oral suspension is not bioequivalent to the film coated tablet is not included	This is important information that should be included	Include a statement that the two dosage forms are not bioequivalent
Full Prescribing Information			
1.	(b) (4)	(b) (4) .	(b) (4)

	[redacted].		[redacted].
2.	Table 2. *Dosing Recommendations for TIVICAY in Pediatric Patients Aged at Least 4 Weeks and Weighing* [redacted]	If a prescriber misinterprets the dosing table for patients weighing [redacted] the patient would receive an overdose.	We recommend a separate table for dosing pediatric patients weighing [redacted]. This will minimize the risk that prescribers incorrectly interpret the proposed table and prescribe [redacted].
3.	The Sponsor includes the 25 mg film coated tablets in Section 16 of the PI, How Supplied/Storage and Handling, but does not include information on how the tablets can be used for doses in Section 2 of the PI, Dosage and Administration.	The inclusion of the tablet in Section 16, but not Section 2 of the PI may lead to confusion.	Consider including the use of the 25 mg tablet in the adult dosing table in Section 2 (i.e. 2 x 25 mg OR 1x 50 mg).

5.2 RECOMMENDATIONS FOR VIIV

Identified Issues and Recommendations for ViiV			
	Identified Issue	Rationale for Concern	Recommendation
Container Labels			
1.	Information to store the tablets in the original container lacks prominence.	Lack of prominence for this information could lead to pharmacists or caregivers dispensing or storing the tablets outside the original container.	Move the statement "Store in the original package to protect from moisture." From the side panel to the principal display panel below the established name and consider bolding the statement or some other means to increase the overall prominence. To make room for this statement, consider decreasing the font of the salt equivalency statement or move the salt equivalency statement to the side panel.
2.	(b) (4)		
3.	Information that the film coated tablets and tablets for oral suspension are not substitutable is not located on the label.	This information is important to minimize the risk of substitution errors during dispensing.	Include the statement: "Tivicay and Tivicay PD are not substitutable." on the principal display panel. Additionally, add a rectangular outline around the text to increase its prominence. To make room

			for this statement, consider decreasing the font of the salt equivalency statement or move the salt equivalency statement to the side panel. We recommend the statement "Tivicay and Tivicay PD are not substitutable." also be added to the currently approved Tivicay container labels. We note the use of the term 'interchangeable' in the PI. Ensure the term used in this statement is consistent with the final terminology in the PI (i.e. interchangeable or substitutable).
4.	The IFU indicates that the tablet for oral suspension should not be chewed, cut, or crushed, but it is not included on the label.	This information could be overlooked if not included on the label.	Include the statement "Do not chew, cut, or crush tablet for oral suspension" on the side panel. This will allow the storage and substitutability statement to maintain prominence.
Carton Labeling			
1.	Information to store the tablets in the original container lacks prominence.	Lack of prominence for this information could lead to pharmacists or caregivers dispensing or storing the tablets outside the original container.	Move the statement "Store in the original package to protect from moisture." From the side panel to the principal display panel below the established name.
2.	The statement "For Pediatric Dosing" is ambiguous to distinguish the non- substitutability of the film	This statement may not be interpreted as intended, leading to an increased risk that the wrong	See Comment #3 for an alternative statement to convey this information.

	coated tablets and tablets for oral suspension.	formulation could be dispensed.	
3.	Information that the film coated tablets and tablets for oral suspension are not substitutable is not located on the carton.	This information is important to minimize the risk of substitution errors during dispensing.	Include the statement: "Tivicay and Tivicay PD are not substitutable." on the principal display panel. Additionally, add a rectangular outline around the text to increase its prominence. We note the use of the term 'interchangeable' in the PI. Ensure the term used in this statement is consistent with the final terminology in the PI (i.e. interchangeable or substitutable).
4.	The IFU indicates that the tablet for oral suspension should not be chewed, cut, or crushed, but it is not included on the carton labeling.	This information could be overlooked if not included on the carton labeling.	Include the statement 'Do not chew, cut, or crush tablet for oral suspension" on the principal display panel.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for Tivicay received on December 12, 2019 from ViiV Healthcare Company (ViiV).

Table 5. Relevant Product Information for Tivicay	
Initial Approval Date	August 13, 2013
Active Ingredient	dolutegravir
Indication	Treatment of HIV infection in adults and pediatric patients at least 4 weeks and weighing at least 3 kg.
Route of Administration	oral
Dosage Form	Proposed: tablets for oral suspension Currently approved: film coated tablets (FCT) Tablets are not bio-equivalent.
Strength	Proposed: 5 mg Currently approved FCT: 10 mg, 25 mg, 50 mg
Dose and Frequency	Tablets for Oral Suspension: 5 mg to 30 mg orally once daily
How Supplied	Bottle of 60 tablets
Storage	Store in the original package to protect from moisture. Keep the bottle tightly closed. Do not remove desiccant.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 27, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, Tivicay and IND 075382. Our search identified 4 previous reviews[e,f,g,h], and we considered our previous recommendations to see if they are applicable for this current review.

[e] Wilson, V. Human Factors Protocol Review for dolutegravir tablets for oral suspension (IND 075382). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018-NOV-19. RCM No.: 2018-1991.

[f] Wilson, V. Human Factors Protocol Review Memorandum for dolutegravir tablets for oral suspension (IND 075382).Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018-DEC-11. RCM No.: 2018-1991-1.

[g] Wilson, V. Human Factors Protocol Review Memorandum for dolutegravir tablets for oral suspension (IND 075382). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019-MAR-18. RCM No.: 2018-1991-2.

[h] Schlick J. Human Factors Protocol Review for dolutegravir tablets for oral suspension (IND 075382). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019-MAY 8. RCM No.: 2019-1991-3.

APPENDIX C. HUMAN FACTORS STUDY

HF Validation Study Report:
\\cdsesub1\evsprod\nda213983\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hiv\5354-other-stud-rep\2019n405076\2019n405076-report.pdf

APPENDIX D. ISMP NEWSLETTERS N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) – N/A

APPENDIX F. INFORMATION REQUEST

IFU Information Request

We sent an Information Request via email on February 12, 2020 and received a response from the Sponsor on February 19, 2020.

The Sponsor indicated in their human factors (HF) validation study report that they intend to revise the IFU after conducting the HF validation study (Section 12.1, See Appendix C for a link to the HF results report document). We asked the Sponsor to indicate if they submitted their intend to market IFU and if the revisions were incorporated in the intend to market IFU. The Sponsor replied that they submitted the intend-to-market IFU with revisions and provided an explanation for the rationale of the revisions. The revisions made to the IFU involved non-critical tasks and, therefore, we determined that new risks to critical tasks were not introduced and do not require conducting another HF validation study.

We also note that the Sponsor also incorporated the recommendations from PLT sent on April 4, 2019 date after the HF validation study was completed. We note the Sponsor received the PLT recommendations after starting the HF validation study prior to April 4, 2019. Additionally, the Sponsor updated the IFU according to the guidance *Patient Labelling for Human Prescription Drug and Biological Products and Drug-Device and Biologic-Device Combination Products— Content and Format (FDA Draft Guidance, July 2019).*

The revisions improve the clarity of the IFU and do not substantially change the IFU that involve critical tasks. Thus, we determined that the revisions do not require conducting another HF validation study.

A link to the Information Request Response document can be found via EDR:
\\cdsesub1\evsprod\nda213983\0006\m1\us\111-information-amendments\cmc-response-12feb2020.pdf

30-Count Bottle and 25 mg Strength Information Request

We identified a medication error concern with the 60 count tablet bottle as the only package configuration and the inclusion of the 25 mg tablet film-coated tablet in Section 16 , How Supplied/Storage and Handling, even though the proposed dosing and administration does not

include the strength to achieve the dose. We sent an IR on March 27, 2020 to gather additional information for these medication error concerns. The Sponsor responded on April 3, 2020. The Information Request can be found at:

\\CDSESUB1\evsprod\nda213983\0012\m1\us\111-information-amendments\response-to-fda-27mar2020-clin-info-request.pdf

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[i] along with postmarket medication error data, we reviewed the following Tivicay labels and labeling submitted by ViiV Healthcare Company (ViiV).

- Container label received on April 24, 2020:
  \\CDSESUB1\evsprod\nda213983\0017\m1\us\114-labeling\1141-draft\draft-5mg-lbl.pdf
- Carton labeling received on April 24, 2020
  \\CDSESUB1\evsprod\nda213983\0017\m1\us\114-labeling\1141-draft\draft-5mg-ctn.pdf
- Instructions for Use received on December 12, 2019
  \\cdsesub1\evsprod\nda213983\0001\m1\us\114-labeling\1141-draft\draft-annotated.pdf
- Patient Information Sheet received on December 12, 2019
  \\cdsesub1\evsprod\nda213983\0001\m1\us\114-labeling\1141-draft\draft-annotated.pdf
- Prescribing Information received on April 24, 2020
  \\CDSESUB1\evsprod\nda213983\0017\m1\us\114-labeling\1141-draft\draft-annotated.pdf

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

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MILLIE B SHAH
05/15/2020 04:26:18 PM

QUYNHNHU T NGUYEN
05/15/2020 04:35:30 PM

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: April 22, 2020

TO: Debra Birnkrant, M.D.
Director
Division of Antivirals (DAV)
Office of Infectious Diseases (OID)
Office of New Drugs (OND)

FROM: Stanley Au, Pharm.D., BCPS
Lead Pharmacologist
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Analytical review-Radboud University Medical Center, Department of Pharmacy, Nijmegen, The Netherlands

1. Review Summary

The Office of Study Integrity and Surveillance (OSIS) was requested by the Division of Antivirals (DAV), OND to inspect the analytical portion of the PENTA-20 (Odyssey) study for NDA 204790 (S25) and NDA 213983 conducted at Radboud University Medical Center, Department of Pharmacy, Nijmegen, The Netherlands.

OSIS was unable to conduct the inspection because of the COVID-19 pandemic. However, I identified issues based on reviewing the PENTA-20 (Odyssey) method validation and bioanalytical reports. At the request of OSIS, these issues were included in an information request to the applicant (ViiV Healthcare).

Based on reviewing the PENTA-20 (Odyssey) method validation and bioanalytical reports plus the information request responses, I conclude that the analytical data is acceptable for the PENTA-20 (Odyssey) trial.

The review division should also note the following corrections listed below for the PENTA-20 bioanalytical report. Items a and b were corrected in the updated PENTA-20 bioanalytical report

that was submitted as part of the IR responses. For item c, I recommend that the review division evaluate whether this correction affects the PENTA-20 dolutegravir pharmacokinetic ana

a) (b) (4)

b)

c)

(b) (4)

2. Reviewed Study

PENTA-20 (Odyssey)
A randomized trial of dolutegravir-based antiretroviral therapy (DTG) vs. standard of care in children with HIV infection starting first-line or switching to second-line ART
Sample Analysis Period: November 29, 2017-December 27, 2018

3. Scope of Review

I reviewed the analytical information that was submitted to the FDA for the PENTA-20 (Odyssey) study conducted at Radboud University Medical Center, Department of Pharmacy, Nijmegen, The Netherlands.

The review included evaluating the PENTA-20 (Odyssey) method validation and bioanalytical reports as well as the responses to an information request related to the PENTA-20 (Odyssey) analytical information.

4. Review Findings

(b) (4)

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cc: OTS/OSIS/Kassim/Folian/Mitchell/Fenty-Stewart/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas
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Draft: SA 4/15/2020, 4/20/2020, 4/21/2020, 4/22/2020
Edit: JC 4/17/2020, 4/21/2020

ECMS:
Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ANALYTICAL/Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

OSIS File #: 8819/FACTS: 11985398

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/s/

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