CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215413Orig1s000

OTHER REVIEW(S)

Division of Antivirals

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 205551/S-028, original NDA 215413

Name of Drug: Triumeq (abacavir, dolutegravir, lamivudine) tablets
Triumeq PD (abacavir, dolutegravir, lamivudine) tablets for oral suspension

Applicant: ViiV Healthcare Company

Submission and Receipt Date: September 30, 2022

Labeling Reviewed

Submission Date: March 28, 2022

Receipt Date: March 28, 2022

Background and Summary Description:

On September 30, 2021, ViiV Healthcare Company submitted NDA 215413 for Triumeq PD (abacavir, dolutegravir, lamivudine) tablets for oral suspension and an efficacy supplement for NDA 205551/S-28, tablets that proposed to expand the patient population to include the treatment of HIV-1 infection in pediatric patients weighing 14 kg to less than 40 kg. The submissions were submitted to fulfill PREA PMR 2768-2 found in the August 22, 2014, Approval Letter for NDA 205551, The data to support the changes was based upon data from BA/BE studies, a food effect study, modeling and simulation data, the ARROW and IMPAACT P1093 studies, and two pharmacokinetic substudies from the ODYSSEY study. Upon review, the Division extended the approved patient population for Triumeq PD, to 10 kg to less than 25 kg.

Instructions for Use and a Warning Card for Triumeq PD were also added to the labeling..

Review

For the purposes of this review, the last approved labeling for NDA 205551/S-026 dated March 23, 2021, was compared to the Applicant's most recent proposed draft version dated March 24, 2022.

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/s/

KEVIN L ALLEN
03/28/2022 11:22:15 AM

KAREN D WINESTOCK
03/29/2022 08:32:07 AM

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

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

Memorandum

Date: March 11, 2022

To: Kevin Allen, Regulatory Project Manager
Division of Antivirals (DAV)

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

CC: Sam Skariah, Team Leader, OPDP

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

NDA: 205551 / S-028
215413

In response to DAV consult request dated October 25, 2021, OPDP has reviewed the proposed product labeling (PI) and Medication Guide for TRIUMEQ (abacavir, dolutegravir, and lamivudine) tablets, for oral use (Triumeq) and TRIUMEQ PD (abacavir, dolutegravir, and lamivudine) tablets for oral suspension (Triumeq PD), and the Instructions for Use (IFU) and carton and container labeling for the original NDA submission for Triumeq PD. This supplement (S-028) proposes dosing recommendations with Triumeq in HIV-1 infected pediatric patients weighing at least 25 kg to less than 40 kg. The original NDA 215413 proposes a new dosage form and dosing to expand the patient population to include the treatment of HIV-1 in pediatric patients weighing at least 14 kg to less than 25 kg.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DAV (Kevin Allen) on March 2, 2022, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide and IFU were sent under separate cover on March 10, 2022.

Carton and Container Labeling: OPDP has reviewed the attached updated proposed carton and container labeling received by electronic mail from DAV (Kevin Allen) on March 10, 2022, and our comments are provided below.

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:	March 10, 2022
To:	Kevin Allen, MS Regulatory Project Manager **Division of Antivirals (DAV)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS 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: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name); Dosage Form and Route; Application Type/Number; Supplement Number:	TRIUMEQ (abacavir, dolutegravir, and lamivudine) tablets, for oral use; NDA 205551/S-028 TRIUMEQ PD (abacavir, dolutegravir, and lamivudine) tablets for oral suspension, NDA 215413
Applicant:	ViiV Healthcare Company c/o GlaxoSmithKline

1 INTRODUCTION

On September 30, 2021, ViiV Healthcare Company c/o GlaxoSmithKline submitted for the Agency's review the following application intended to fulfill PMR 2768-2:

- Prior Approval Supplement (PAS) – Efficacy to approved New Drug Application (NDA) 205551/S-028 for TRIUMEQ (abacavir, dolutegravir, and lamivudine) tablets. This supplement proposes dosing recommendations with TRIUMEQ in HIV-1 infected pediatric patients weighing at least 25 kg to less than 40 kg.
- Original NDA 215413 for TRIUMEQ PD (abacavir, dolutegravir, and lamivudine) tablets for oral suspension. With this submission the Applicant proposes a new dosage form and dosing to expand the patient population to include the treatment of HIV-1 in pediatric patients weighing at least 14 kg to less than 25 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 October 25, 2021, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TRIUMEQ (abacavir, dolutegravir, and lamivudine) tablets and TRIUMEQ PD (abacavir, dolutegravir, and lamivudine) tablets for oral suspension, and Instructions for Use (IFU) for TRIUMEQ PD (abacavir, dolutegravir, and lamivudine) tablets for oral suspension.

A separate Division of Medication Error, Prevention, and Analysis (DMEPA) review of the TRIUMEQ PD (abacavir, dolutegravir, and lamivudine) tablets for oral suspension IFU was completed on January 25, 2022.

2 MATERIAL REVIEWED

- Draft TRIUMEQ (abacavir, dolutegravir, and lamivudine) tablets and TRIUMEQ PD (abacavir, dolutegravir, and lamivudine) tablets for oral suspension MG and IFU for TRIUMEQ PD (abacavir, dolutegravir, and lamivudine) tablets for oral suspension received on September 30, 2021 and October 5, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 2, 2022.
- Draft TRIUMEQ (abacavir, dolutegravir, and lamivudine) tablets and TRIUMEQ PD (abacavir, dolutegravir, and lamivudine) tablets for oral suspension Prescribing Information (PI) received on September 30, 2021 and October 5, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 2, 2022.

3 REVIEW METHODS

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

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

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG 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 MG and IFU are 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 MG and IFU.

Please let us know if you have any questions.

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/s/

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WENDY R LUBARSKY
03/10/2022 04:25:55 PM

BARBARA A FULLER
03/10/2022 06:58:49 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	March 9, 2022
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 215413 NDA 205551/S-28
Product Name and Strength:	Triumeq PD (abacavir, dolutegravir, and lamivudine) Tablet for Oral Suspension, 60 mg/5 mg/30 mg Triumeq (abacavir, dolutegravir, and lamivudine) Tablet, 600 mg/50 mg/300 mg
Applicant/Sponsor Name:	ViiV Healthcare Company (ViiV)
OSE RCM #:	2021-1944-1
DMEPA 1 Safety Evaluator:	Melina Fanari, R.Ph
DMEPA 1 Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on March 1, 2022 for Triumeq PD Tablets for oral suspension (abacavir, dolutegravir, and lamivudine) and Triumeq (abacavir, dolutegravir, and lamivudine) Tablets. The Division of Antivirals (DAV) requested that we review the revised container labels and carton labeling for Triumeq PD Tablets for oral suspension (abacavir, dolutegravir, and lamivudine) and Triumeq (abacavir, dolutegravir, and lamivudine) Tablets (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

[a] Fanari, M. Label and Labeling Review for Triumeq PD Tablets for oral suspension (abacavir, dolutegravir, and lamivudine) and Triumeq (abacavir, dolutegravir, and lamivudine) Tablets (N). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 Jan 25. RCM No.: 2021-1944.

2 CONCLUSION

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

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/s/

MELINA N FANARI
03/09/2022 12:25:59 PM

SEVAN H KOLEJIAN
03/09/2022 12:29:12 PM

LABEL AND LABELING REVIEW

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

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

Date of This Review:	January 25, 2022
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 215413 NDA 205551/S-28
Product Name, Dosage Form, and Strength:	Triumeq PD (abacavir, dolutegravir, and lamivudine) Tablet for Oral Suspension, 60 mg/5 mg/30 mg Triumeq (abacavir, dolutegravir, and lamivudine) Tablet, 600 mg/50 mg/300 mg
Product Type:	Combination and Multi-Ingredient Products
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	ViiV Healthcare Company (ViiV)
FDA Received Date:	September 30, 2021
OSE RCM #:	2021-1944
DMEPA Safety Evaluator:	Melina Fanari, R.Ph
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 REASON FOR REVIEW

As part of the approval process for Triumeq PD Tablets for oral suspension (abacavir, dolutegravir, and lamivudine) (NDA 215413) and Triumeq (abacavir, dolutegravir, and lamivudine) Tablets (NDA 205551/S-028) the Division of Antivirals (DAV) requested that we review the proposed prescribing information (PPI), medication guide (MG), warning card, instruction for use (IFU), container label and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

Triumeq tablet (NDA 205551) was approved on August 22, 2014 for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 40 kg.

On September 30, 2021, ViiV submitted a new tablet for oral suspension formulation, Triumeq PD (abacavir, dolutegravir, and lamivudine) to propose dosing recommendations in HIV-1 infected pediatric patients weighing at least 25 kg to less than 40 kg.

DMEPA previously evaluated the proposed Triumeq PD convenience kit for marketing and determined that a human factors validation study was not needed as part of the NDA submission.[a] This determination was made due to the bridging justification of HF data from the Tivicay PD approved NDA (204790). Of note, the original proposed user interface under IND 114820 included a syringe for infant administration (in addition to the dosing cup) which is not proposed in the current Triumeq PD NDA submission since the proposed dosing in labeling is for pediatric patients >14 kg. The Tivicay NDA includes both the dosing cup and syringe.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Review

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

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

[a] Shaw, M. Use-Related Risk Analysis Review for abacavir, dolutegravir, and lamivudine (IND 114820). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Dec 4. RCM No.: 2019-1896.

3 CONCLUSION AND RECOMMENDATIONS

The approval of Triumeq PD tablets for oral suspension will extend the current abacavir, dolutegravir, and lamivudine product line (Triumeq Tablets) to include dosing in HIV-1 infected pediatric patients weighing at least 25 kg to less than 40 kg. Triumeq PD tablets for oral suspension and Triumeq Tablets are not bioequivalent and interchangeable on a milligram-per-milligram basis due to differing pharmacokinetic profiles for the dolutegravir component. The proposed PI, container label, carton labeling and IFU may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for ViiV Healthcare Company. We collaborated with the review team to revise the PI and have no proposed recommendation to the IFU and MG.

4 RECOMMEDATIONS FOR DIVISION OF ANTIVIRALS (DAV)

Table 1. Identified Issues and Recommendations for Division of Antivirals (DAV)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The 'Do not interchange TRIUMEQ tablets and TRIUMEQ PD tablets for oral suspension on a milligram-per-milligram basis due to differing pharmacokinetic profiles for the dolutegravir component' statement lacks prominence in section 2.	Minimize wrong drug medication errors.	Relocate this statement from section 2.5 to section 2.3
2.	Administration instructions precede the dosage table in section 2.4	Minimize wrong administration medication errors.	The 'Administer TRIUMEQ PD tablets for oral suspension with or without food' statement in section 2.4 should be relocated after the dosage chart.
Full Prescribing Information – Section 17 Patient Counseling			
	Reference to IFU is missing.	Ensure proposer product preparation and administration.	Add a statement in the administration Instructions section to Instruct caregivers to

Table 1. Identified Issues and Recommendations for Division of Antivirals (DAV)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			the read the Instruction for Use.

5 RECOMMENDATIONS FOR VIIV HEALTHCARE COMPANY

Table 2. Identified Issues and Recommendations for ViiV Healthcare Company (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Container Label(s) and Carton Labeling			
1.	Proprietary name lacks sufficient prominence.	Minimize wrong drug medication errors.	Increase the prominence of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
2.	The statement 'Do not chew, cut, or crush tablet' lacks sufficient prominence.	Minimize wrong administration medication errors.	Increase the prominence of the statement 'Do not chew, cut, or crush tablet' by the use of a different color than black.
3.	The statement 'Triumeq and Triumeq PD are not interchangeable' lacks sufficient prominence.	Minimize wrong drug medication errors.	Increase the prominence of the statement 'Triumeq and Triumeq PD are not interchangeable' with the use of a different color than black. In addition, a draft container label and carton labeling incorporating this statement should be submitted to NDA 205551/S-28.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Triumeq PD and Triumeq received on September 30, 2021 from ViiV Healthcare Company.

Table 1. Relevant Product Information for Triumeq PD and Triumeq

<table>
<tr><th></th><th>Triumeq PD (proposed NDA 215413)</th><th>Triumeq (NDA 205551)</th></tr>
<tr><td>Active Ingredient</td><td colspan="2">abacavir, dolutegravir, and lamivudine</td></tr>
<tr><td>Indication of Use</td><td colspan="2">intended as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in pediatric and adult patients</td></tr>
<tr><td>Route of Administration</td><td colspan="2">Oral</td></tr>
<tr><td>Dosage Form</td><td>Tablet for Oral Suspension</td><td>Tablet</td></tr>
<tr><td>Strength</td><td>60 mg/5 mg/30 mg</td><td>600 mg/50 mg/300 mg</td></tr>
<tr><td>Dose and Frequency</td><td>
<table>
<tr><th rowspan="2">Pediatric Population Body Weight</th><th colspan="2">TRIUMEQ PD Tablets for Oral Suspension</th></tr>
<tr><th>Recommended Daily Dose</th><th>Number of Tablets</th></tr>
<tr><td>14 kg to <20 kg</td><td>300 mg ABC, 25 mg DTG, and 150 mg 3TC</td><td>5</td></tr>
<tr><td>20 kg to <25 kg</td><td>360 mg ABC, 30 mg DTG, and 180 mg 3TC</td><td>6</td></tr>
</table>
</td><td>One tablet once daily</td></tr>
<tr><td>How Supplied</td><td>Bottle of 90 tablets with child-resistant closure. Each bottle is packaged with one 40-mL dosing cup.</td><td>Bottles of 30 tablets</td></tr>
<tr><td>Storage</td><td>Store below 30°C (86°F). Store and dispense in the original bottle, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant.</td><td>Store at 25°C (77°F); excursions permitted 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature].</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 12, 20221, we searched for previous DMEPA reviews relevant to this current review using the terms, Triumeq and Triumeq PD. Our search did not identify any reviews with outstanding recommendations.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

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

- Container label, carton labeling and warning card for Triumeq PD received September 30, 20221 (see images below)
- Prescribing Information, Medication Guide, and Instruction for Use received on September 30, 20221 for:
    - Triumeq PD available from \\CDSESUB1\evsprod\NDA215413\0001\m1\us\114-labeling\1141-draft

- Prescribing Information received on September 30, 20221 for:
    - Triumeq available from \\CDSESUB1\evsprod\NDA205551\0183\m1\us\114-labeling\1141-draft

F.2 Label and Labeling Images

Container Label

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

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