Cross-Discipline Team Leader Review

Date	March 23, 2022
From	Su-Young Choi, Pharm.D., Ph.D
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	NDA 205551/S-028 (TRIUMEQ) NDA 215413 (TRIUMEQ PD)
Applicant	ViiV Healthcare Company
Date of Submission	9/30/2021
PDUFA Goal Date	3/30/2022
Proprietary Name	TRIUMEQ, TRIUMEQ PD
Established or Proper Name	Abacavir (ABC), lamivudine (3TC), dolutegravir (DTG)
Dosage Form(s)	TRIUMEQ tablet: ABC/DTG/3TC 600 mg/50 mg/300 mg TRIUMEQ PD, tablet for oral suspension: ABC/DTG/3TC 60 mg/5 mg/30 mg
Applicant Proposed Indication(s)/Population(s)	For the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and in pediatric patients weighing at least 14 kg
Applicant Proposed Dosing Regimen(s)	For adults and pediatric patients weighing 25 kg and above: one TRIUMEQ tablet once daily For pediatrics: weight based dosing with TRIUMEQ PD
Recommendation on Regulatory Action	*Approval*
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and in pediatric patients weighing at least 10 kg
Recommended Dosing Regimen(s) (if applicable)	For adults and pediatric patients weighing 25 kg and above: one TRIUMEQ tablet once daily For pediatrics: weight based dosing with TRIUMEQ PD

1. Benefit-Risk Assessment

TRIUMEQ is a fixed dose combination of dolutegravir (DTG, integrase strand transfer inhibitor), abacavir (ABC, nucleoside analogue reverse transcriptase inhibitor), and lamivudine (3TC, nucleoside analogue reverse transcriptase inhibitor) for the treatment of HIV-1 infection. The Applicant submitted the current applications to extend the indication to pediatric patients weighing 14 kg and above. For the use in pediatric patients, the Applicant developed a new pediatric formulation, TRIUMEQ PD, tablet for oral suspension.

No new clinical safety and efficacy data in pediatric patients were submitted. The safety and efficacy of the individual components were previously established with TIVICAY (dolutegravir), EPIVIR (lamivudine), and ZIAGEN (abacavir) in pediatric patients. All of the components of TRIUMEQ and TRIUMEQ PD have been approved for pediatric patients down

to infants. The relative bioavailability study results support bridging the safety and efficacy established with the individual products to TRIUMEQ PD. No new or unique safety and efficacy signals are anticipated with TRIUMEQ PD.

There are several once daily, single tablet fixed-dose combination (FDC) products available for adults and older pediatric patients. However, FDC products for pediatric patients who cannot swallow tablets are limited in the U.S. at this time. TRIUMEQ PD is the first fixed dose combination pediatric formulation that can be used as a once daily, complete regimen. In addition, individual components of TRIUMEQ are recognized as preferred antiretrovirals (ARVs) for the initial therapy in ARV-naïve children by the current HHS HIV treatment guideline. Therefore, it is expected that many pediatric patients would benefit from the availability of the product allowing once daily simplified dosing upon the approval of TRIUMEQ PD. Refer to the clinical review by Dr. Amy Bishara for full details on the risk-benefit analysis.

In conclusion, the review team has determined that the benefits of TRIUMEQ and TRIUMEQ PD outweigh the risks and recommends the approval. The review team also reviewed the available safety, efficacy, and PK data of the individual components and concluded that the indication can be extended to patients who weigh 10 kg.

2. Background

TRIUMEQ is currently approved in adults and pediatric patients 12 years and older and weighing at least 40 kg. In this application, the Applicant proposed an extension of the indication to pediatric patients weighing 14 kg and above with a new pediatric formulation, TRIUMEQ PD (tablet for oral suspension). The proposed approach for the approval of TRIUMEQ PD is bridging the safety and efficacy of the individual products that was previously established by demonstrating comparable relative bioavailability for the individual components between TRIUMEQ PD and the individual products. To support the approval, the Applicant submitted the following studies.

- Study 205894: a relative bioavailability study that compared TRIUMEQ PD to TRIUMEQ tablets in healthy adults
- Study 216149: a food effect study with TRIUMEQ PD
- Study 200402: a relative bioavailability study comparing DTG/ABC/3TC tablet for oral suspension when dispersed and consumed under different dosing conditions
- Population pharmacokinetic (PopPK) modeling and simulation results supporting the proposed dosing regimens

The individual components of TRIUMEQ and TRIUMEQ PD have been approved in pediatric patients. The proposed dosing regimen of TRIUMEQ PD and the approved dosing regimens of DTG, ABC, and 3TC with individual products are summarized below.

Table 1. Proposed dosing regimen of TRIUMEQ and TRIUMEQ PD in pediatric patients weighing ≥10 kg and approved daily dosing of DTG, ABC, and 3TC with individual products

Body weight	Proposed daily dosing with TRIUMEQ PD or TRIUMEQ	Approved daily dosing with individual tablet products	Approved daily dosing with individual ABC, 3TC solution products
≥10 to < 14 kg	4 PD tablets DTG: 20 mg ABC: 240 mg 3TC: 120 mg	Not approved with tablet formulations	DTG: 20 mg (TIVICAY PD) ABC: 160–224 mg (ZIAGEN solution) 3TC: 100–140 mg (EPIVIR solution)
≥14 to < 20 kg	5 PD tablets DTG: 25 mg ABC: 300 mg 3TC: 150 mg	DTG: 40 mg (TIVICAY tablet) ABC: 300 mg (ZIAGEN tablet) 3TC: 150 mg (EPIVIR tablet)	DTG: 25 mg (TIVICAY PD) ABC: 224–320 mg (ZIAGEN solution) 3TC: 140–200 mg (EPIVIR solution)
≥20 to < 25 kg	6 PD tablets DTG: 30 mg ABC: 360 mg 3TC: 180 mg	DTG: 50 mg (TIVICAY tablet) ABC: 450 mg (ZIAGEN tablet) 3TC: 225 mg (EPIVIR tablet)	DTG: 30 mg (TIVICAY PD) ABC: 320–400 mg (ZIAGEN solution) 3TC: 200–250 mg (EPIVIR solution)
≥ 25 kg	1 TRIUMEQ tablet DTG: 50 mg ABC: 600 mg 3TC: 300 mg	DTG: 50 mg (TIVICAY tablet) ABC: 600 mg (ZIAGEN tablet or solution) 3TC: 300 mg (EPIVIR tablet or solution)	

- TIVICAY PD is approved in pediatric patients aged at least 4 weeks and weighing at least 3 kg.
- ZIAGEN and EPIVIR are approved in pediatric aged at least 3 months. The dosing regimens of ZIAGEN and EPIVIR solutions in pediatric patients are 16 mg/kg/day and 10 mg/kg/day, respectively.

Refer to the clinical review by Dr. Amy Bishara for additional background information on:
- Currently available options for HIV treatment in adults and children
- Regulatory history of TRIUMEQ
- Summary of safety and efficacy data supporting the previous approval of ZIAGEN, EPIVIR, EPVIZOM, and TIVICAY in adults and pediatrics

3. Product Quality

TRIUMEQ Tablet

No new information was submitted in relation to the full strength tablet.

TRIUMEQ PD

TRIUMEQ PD film-coated tablet for oral suspension contains 60 mg of ABC, 5 mg of DTG, and 30 mg of 3TC. The Office of Pharmaceutical Quality has determined that the information submitted by the Applicant in this supplement is acceptable and recommends approval. Refer to the review of Chemistry, Manufacturing, and Control (CMC) for NDA215413 for full details.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology data were submitted.

5. Clinical Pharmacology

Refer to the clinical pharmacology review by Dr. Yang Zhao for full details. The submitted clinical pharmacology data support the approval of TRIUMEQ and TRIUMEQ-PD in pediatric patients weighing 10 kg and above.

Comparable relative bioavailability between TRIUMEQ PD and individual products (TIVICAY PD, ZIAGEN, and EPIVIR) has been demonstrated in Study 205894. Therefore, the pediatric dosing regimens of TIVICAY-PD, ZIAGEN, and EPIVIR can be translated to the pediatric dosing regimens of TRIUMEQ PD without adjusting for differences in relative bioavailability.

The proposed dosing regimens of TRIUMEQ and TRIUMEQ PD (Table 1) are similar to those approved with individual products; for DTG, the proposed dosing regimens for all weight bands with TRIUMEQ PD or TRIUMEQ are identical to those approved with TIVICAY PD or TIVICAY. For ABC and 3TC, the proposed dosing regimens are identical to those approved with individual products for ≥ 25 kg and ≥ 14 to < 20 kg. For ≥ 20 to < 25 kg, the proposed doses (360 mg for ABC and 180 mg for 3TC) with TRIUMEQ PD are slightly lower than the approved doses with the individual products (450 mg with ZIAGEN tablet and 225 mg with EPIVIR tablet). However, predicted concentrations of ABC and 3TC with the proposed dosing regimens are within the range of the observed exposures at the recommended doses of approved products in both pediatrics and adults. For ≥10 to < 14 kg, the proposed dose for ABC (240 mg) with TRIUMEQ PD is slightly higher than the approved dose of ABC (160–224 mg with ZIAGEN solution), but the predicted exposures do not exceed those observed in pediatric patients of other weight bands.

The results of food effect study support the administration of TRIUMEQ PD with or without food.

6. Clinical Microbiology

No new clinical microbiology data were submitted for review.

7. Clinical/Statistical- Efficacy

No new clinical efficacy data were submitted for review. Refer to the clinical review by Dr. Amy Bishara and the USPIs of the individual products for data supporting the efficacy of the individual products (TIVICAY PD, EPIVIR, and ZIAGNEN) in pediatric patients.

8. Safety

In addition to the previously reviewed safety data with the individual products (TIVICAY PD, EPIVIR, and ZIAGEN), interim safety data from the ongoing clinical trial IMPAACT P2019 were reviewed. While safety data from IMPAACT P2019 are limited at this time, findings are generally similar to what have been previously reported with the individual products. There was one report of Grade 4 drug induced liver injury in a 7-year-old male after 36 weeks of dosing. The study drug was permanently discontinued, and the event was considered drug-related by the clinical investigator and the study sponsor. One month later, the study site considered the event resolved. It is likely the elevated LFTs were related to the ABC and DTG components. Of note, the TRIUMEQ label already mentions the potential for hepatotoxicity in adults, and this case does not preclude the approval of TRIUMEQ PD in pediatric patients.

Refer to the clinical review by Dr. Amy Bishara for full details.

9. Advisory Committee Meeting

An Advisory Committee meeting was not held. There was no significant issue to warrant a public discussion.

10. Pediatrics

Currently, there are two outstanding PREA PMRs under NDA 205551.

PMR 2768-1
Conduct a pediatric trial to evaluate the pharmacokinetics, safety and antiviral activity (efficacy) of abacavir/dolutegravir/lamivudine FDC tablets in HIV infected pediatric participants 2 years to less than 6 years of age. The safety and antiviral activity (efficacy) of abacavir/dolutegravir/lamivudine FDC tablets in pediatric participants should be evaluated for a minimum of 24 weeks.

PMR 2768-2
Conduct a pediatric trial to evaluate the pharmacokinetics, safety and antiviral activity (efficacy) of abacavir/dolutegravir/lamivudine FDC tablets in HIV infected pediatric participants 6 years to less than 12 years of age and in children older than 12 years of age who weigh less than 40 kg. The safety and antiviral activity (efficacy) of abacavir/dolutegravir/lamivudine FDC tablets in pediatric participants should be evaluated for a minimum of 24 weeks.

(b) (4)

The review team concluded that PMR-2768-2 has been fulfilled with the current sNDA application, but PMR 2768-1 should not be considered fulfilled at this time. The information contained in this sNDA was presented before the Pediatric Review Committee (PeRC) on

March 1, 2022. PeRC agreed with Division's conclusions. In addition, the approval of TRIUMEQ PD formulation triggers PREA PMR as a new dosage form. As of this writing, the review team is in the process of issuing a new PREA PMR. The new PREA PMR will be the same with PMR 2768-2, but tied to NDA 215413.

Of note, it is expected that the ongoing trial, IMPAACT P2019, is expected to provide data to fulfill remaining PMR and WR.

11. Other Relevant Regulatory Issues

There are no outstanding regulatory issues at this time.

12. Labeling

Below is a high-level summary of the main changes made to the TRIUMEQ USPI based on this supplemental NDA. Refer to the final approved labeling for full details.

Section 1. Indications and Usage

- The indication has been extended to include pediatric patients weighing at least 10 kg.

Section 2. Dosage and Administration

- The dosage recommendations for pediatric patients for each weight band have been added.

- The overview of TRIUMEQ doseage forms has been added. This section provides the following information:
    - Do not interchange TRIUMEQ tablets and TRIUMEQ PD for oral suspension on a milligram-per-milligram basis due to differing pharmacokinetic profiles for the dolutegravir component.
    - Because TRIUMEQ PD is a fixed-dose tablet and the dosage of individual components cannot be adjusted, it may lead to suboptimal dosing for patients weighing > 25 kg.
- A brief description on the instructions for dispersion have been added.
- Dosing recommendations with concomitant medications and for subjects with renal impairment have been updated to include pediatric patients weighing 10 kg and above.

Section 3. Dosage Forms and Strengths

- The description of TRIUMEQ PD tablet for oral suspension has been added.

Section 5. Warnings and Precautions

- Section 5.8, Different Formulations Are Not Interchangeable has been added. This has been added to be consistent with TIVICAY USPI.

Section 6. Adverse Reactions
- The pediatric subsection has been added to reflect adverse events observed with EPIVIR, ZIAGEN, EPZICOM, TIVICAY, and TIVICAY PD.

Section 7. Drug Interactions
- For concomitant medications requiring an additional TIVICAY or TIVICAY PD dose separated by 12 hours from TRIUMEQ (fosamprenavir/ritonavir, tipranavir/ritonavir, carbamazepine, or rifampin), dolutegravir dosing for each weight band for pediatric patients has been added.

Section 8. Use in Specific Populations
- The pediatric subsection (8.4) has been updated to provide the summary of the clinical data supporting use of TRIUMEQ and TRIUMEQ PD in pediatric patients with HIV-1 infection weighing at least 10 kg, derived from the previously conducted pediatric trials using the individual components.

Section 12. Clinical Pharmacology
- A summary of the relative bioavailability study and the food effect study results has been added.
- A summary of the pharmacokinetic data with the individual components has been added.

Section 14. Clinical Studies
- The efficacy of the individual components in pediatric patients has been added.

All of the safety, efficacy, and PK of the individual components added to TRIUMEQ USPI described above are based on the USPIs of individual components. In addition to the changes related to the new pediatric indication, minor edits have been made regarding exacerbation of hepatitis B and the Antiretroviral Pregnancy Registry to be consistent with the most recent USPIs of the individual components.

13. Postmarketing Recommendations

The multidiscipline review team did not raise any new concerns that would warrant a new PMR or PMC. See Section 10 of this review for PREA PMR.

14. Recommended Comments to the Applicant

No additional comments need to be communicated to the Applicant at this time.

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