Department of Health and Human Services
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	December 2, 2024
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Product Names:	Triumeq tablet, Triumeq PD tablet for oral suspension (abacavir, dolutegravir, lamivudine)
Pediatric Labeling Approval Dates:	March 30, 2022 and June 15, 2023
Application Type/Numbers:	NDA 205551 and NDA 215413
Applicant:	ViiV Healthcare
TTT Record ID:	2024-11322

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Triumeq and Triumeq PD (abacavir, dolutegravir, lamivudine) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with Triumeq and Triumeq PD in pediatric patients.

Triumeq is a three-drug, fixed-dose combination of dolutegravir (DTG), a human immunodeficiency virus type 1 integrase strand transferase inhibitor, and abacavir (ABC) and lamivudine (3TC), both of which are HIV-1 nucleoside analogue reverse transcriptase inhibitors. Triumeq was initially approved in the U.S. on August 22, 2014, and is currently indicated for the treatment of HIV-1 infection in adult and pediatric patients. Triumeq PD is a tablet formulation for oral suspension; each tablet contains 60 mg of ABC, 5 mg of DTG, and 30 mg of 3TC.[1] The Triumeq PD formulation was approved on March 30, 2022.[1]

This pediatric postmarketing safety review was stimulated by the pediatric labeling changes on March 30, 2022, and June 15, 2023, that extended the Triumeq and Triumeq PD indication to include use in pediatric patients aged at least 3 months and weighing at least 6 kg. Additional labeling changes relevant to pediatric patients included pharmacokinetic data and long-term safety and antiviral activity from the Clinical Study IMPAACT 2019.

DPV reviewed all U.S. serious FAERS reports with Triumeq and Triumeq PD in pediatric patients less than 18 years of age from March 14, 2020, through October 10, 2024, and identified four reports; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with Triumeq and Triumeq PD in pediatric patients less than 18 years of age.

DPV will continue routine pharmacovigilance monitoring.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Triumeq and Triumeq PD (abacavir, dolutegravir, lamivudine) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with Triumeq in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Triumeq is a three-drug, fixed-dose combination of dolutegravir (DTG), a human immunodeficiency virus type 1 integrase strand transferase inhibitor, and abacavir (ABC) and lamivudine (3TC), both of which are HIV-1 nucleoside analogue reverse transcriptase inhibitors. It was initially approved in the U.S. on August 22, 2014, and is currently indicated for the treatment of HIV-1 infection in adult and pediatric patients aged at least 3 months and weighing at least 6 kg.[1] Triumeq contains 600 mg of ABC, 50 mg of DTG and 300 mg of 3TC.[1] Triumeq PD is a tablet formulation for oral suspension; each tablet contains 60 mg of ABC, 5 mg of DTG, and 30 mg of 3TC.[1] The Triumeq PD formulation was approved on March 30, 2022.[1]

Pediatric related labeling changes for Triumeq since initial approval are summarized in **Table 1**.[1-4]

Table 1. Summary of Pediatric Related Labeling Changes for Triumeq

Date	NDA and Supplement	Tradename	Labeling Change
11/21/17	NDA 205551	Triumeq	Expanded indication to include pediatric patients weighing at least 40 kg
03/30/22	NDA 215413	Triumeq PD	PD formulation approved for use in pediatric patients weighing 10 kg to less than 25 kg
03/30/22	NDA 205551/0028	Triumeq	Expanded indication to include pediatric patients weighing 25 kg to less than 40 kg
06/15/23	NDA 205551/0031, NDA 215413/0002	Triumeq, Triumeq PD	Expanded indication of Triumeq PD to include pediatric patients aged at least 3 months and weighing at least 6 kg

On July 14, 2020, DPV completed a review of postmarketing adverse event reports with a serious outcome for Triumeq in pediatric patients. DPV's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with Triumeq.[5] On September 1, 2020, DPV's evaluation was presented to the Pediatric Advisory Committee via webposting.

This pediatric postmarketing safety review was stimulated by pediatric labeling changes on March 30, 2022, and June 15, 2023, which extended the Triumeq and Triumeq PD

indication to include use in pediatric patients aged at least 3 months and weighing at least 6 kg.[1,3]

Additional labeling changes included pharmacokinetic data and long-term safety and antiviral activity from the Clinical Study IMPAACT 2019 (NCT03760458).[6] IMPAACT 2019 was a phase I/II, open-label, non-comparative dose confirmation study of Triumeq in children less than 12 years who were antiretroviral treatment (ART) naïve or ART-experienced and virologically suppressed on ART for at least 6 months. Participants weighing 6 kg to less than 25 kg received Triumeq PD and participants weighing 25 kg to less than 40 kg received Triumeq. Dose confirmation, based on pharmacokinetic targets from historical data, was met for all weight groups. No drug-related adverse events were grade 3 or higher, life-threatening or resulted in Triumeq or Triumeq PD discontinuation. At Week 24, all ART-experienced participants and 2/3 ART-naïve participants were virologically suppressed.

1.2 Relevant Labeled Safety Information

The Triumeq and Triumeq PD labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional Triumeq and Triumeq PD labeling information, please refer to the full prescribing information.[4]

WARNING: HYPERSENSITIVITY REACTIONS, AND EXACERBATIONS OF HEPATITIS B

See full prescribing information for complete boxed warning.

Hypersensitivity Reactions

- **Serious and sometimes fatal hypersensitivity reactions have occurred with abacavir-containing products. (5.1)**
- **Hypersensitivity to abacavir is a multi-organ clinical syndrome. (5.1)**
- **Patients who carry the HLA-B*5701 allele are at a higher risk of experiencing a hypersensitivity reaction to abacavir. (5.1)**
- **TRIUMEQ and TRIUMEQ PD are contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients. (4)**
- **Discontinue TRIUMEQ or TRIUMEQ PD as soon as a hypersensitivity reaction is suspected. Regardless of HLA-B*5701 status, permanently discontinue TRIUMEQ or TRIUMEQ PD if hypersensitivity cannot be ruled out, even when other diagnoses are possible. (5.1)**
- **Following a hypersensitivity reaction to TRIUMEQ or TRIUMEQ PD, NEVER restart TRIUMEQ, TRIUMEQ PD, or any other abacavir-containing product. (5.1)**

Exacerbations of Hepatitis B

- **All patients with HIV-1 should be tested for the presence of hepatitis B virus (HBV) prior to or when initiating TRIUMEQ or TRIUMEQ PD. Emergence of lamivudine-resistant HBV variants associated with lamivudine-containing antiretroviral regimens has been reported. If TRIUMEQ or TRIUMEQ PD is used in patients co-infected with HIV-1 and HBV, additional treatment should be considered for appropriate treatment of chronic HBV; otherwise, consider an alternative regimen.**
- **Severe acute exacerbations of HBV have been reported in patients who are co-infected with HBV and HIV-1 and have discontinued lamivudine, a component of TRIUMEQ and TRIUMEQ PD. Closely monitor hepatic function in these patients and, if appropriate, initiate anti-HBV treatment. (5.2)**

---------- CONTRAINDICATIONS ----------

- Presence of HLA-B*5701 allele. (4)
- Prior hypersensitivity reaction to abacavir, dolutegravir, or lamivudine. (4)
- Coadministration with dofetilide. (4)
- Moderate or severe hepatic impairment. (4, 8.7)

---------- WARNINGS AND PRECAUTIONS ----------

- Hepatotoxicity has been reported in patients receiving a dolutegravir-containing regimen. Monitoring for hepatotoxicity is recommended. (5.3)
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. (5.4)
- Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. (5.6)
- TRIUMEQ tablets and TRIUMEQ PD tablets for oral suspension are not interchangeable. (2.3, 5.8)

---------- ADVERSE REACTIONS ----------

The most commonly reported adverse reactions of at least moderate intensity and incidence at least 2% (in those receiving TRIUMEQ) were insomnia, headache, and fatigue. (6.1)

---------- USE IN SPECIFIC POPULATIONS ----------

- Pediatrics: Not recommended for patients aged <3 months or weighing <6 kg. (8.4)
- TRIUMEQ and TRIUMEQ PD are not recommended in patients with creatinine clearance less than 30 mL/min and pediatric patients with a similar degree of renal impairment based on age-appropriate assessment of renal function. (8.6)
- If a dose reduction of abacavir, a component of TRIUMEQ and TRIUMEQ PD, is required for patients with mild hepatic impairment, then the individual components should be used. (8.7)

8.4 Pediatric Use

The clinical data supporting use of TRIUMEQ and TRIUMEQ PD in pediatric patients with HIV-1 infection aged at least 3 months and weighing at least 6 kg is derived from the following previously conducted pediatric trials using TRIUMEQ and TRIUMEQ PD or the individual components:

- The safety, pharmacokinetics, and antiviral activity (efficacy) of TRIUMEQ and TRIUMEQ PD were established through an open-label, multicenter clinical trial (IMPAACT 2019), in which HIV-1–infected, treatment-naive or treatment-experienced, pediatric subjects younger than 12 years and weighing at least 6 kg to less than 40 kg were treated with TRIUMEQ or TRIUMEQ PD *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.2)]*.
- The safety and efficacy of once-daily abacavir and lamivudine were established with a randomized, multicenter trial (ARROW [COL105677]) in HIV-1–infected, treatment-naïve subjects aged 3 months to 17 years with a first-line regimen containing abacavir and lamivudine, using either the combination of EPIVIR and ZIAGEN or EPZICOM *[see Adverse Reactions (6.1), Clinical Studies (14.2)]*.
- The safety, pharmacokinetics, and antiviral activity (efficacy) of TIVICAY and TIVICAY PD were established through an ongoing, open-label, multicenter, dose-finding clinical trial (IMPAACT P1093), in which HIV-1–infected, treatment-naive or treatment-experienced, INSTI-naive, pediatric and adolescent subjects aged 4 weeks to <18 years and weighing at least 3 kg were treated with TIVICAY or TIVICAY PD plus optimized background therapy *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.2)]*.
- Additional pharmacokinetics data were evaluated in 2 pharmacokinetic substudies in ODYSSEY, an ongoing open-label, randomized, non-inferiority trial to evaluate the safety, efficacy, and pharmacokinetic parameters of TIVICAY or TIVICAY PD plus two nucleoside reverse transcriptase inhibitor (NRTIs) (mainly abacavir and lamivudine) compared with standard of care in HIV-1–infected pediatric subjects younger than 18 years *[see Clinical Pharmacology (12.3)]*.

Overall, the safety, and efficacy profile of TRIUMEQ and TRIUMEQ PD in pediatric patients is comparable to that observed in adults. There are no data available on the use of lamivudine in pediatric patients with renal impairment *[see Dosage and Administration (2.7), Warnings and Precautions (5.3), Adverse Reactions (6.1), Use in Specific Populations (8.6), Clinical Pharmacology (12.3), Clinical Studies (14.2)]*.

The safety and effectiveness of TRIUMEQ PD have not been established in pediatric patients aged less than 3 months or weighing less than 6 kg.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 2**.

Table 2. FAERS Search Strategy*	
Date of search	October 11, 2024
Time period of search	March 14, 2020† - October 10, 2024
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product active ingredient: abacavir sulfate/dolutegravir sodium/lamivudine
MedDRA search terms (Version 27.0)	All Preferred Terms
* See **Appendix A** for a description of the FAERS database. † The FAERS search period for the most recently completed DPV pediatric postmarketing pharmacovigilance review for Triumeq ended on March 13, 2020. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

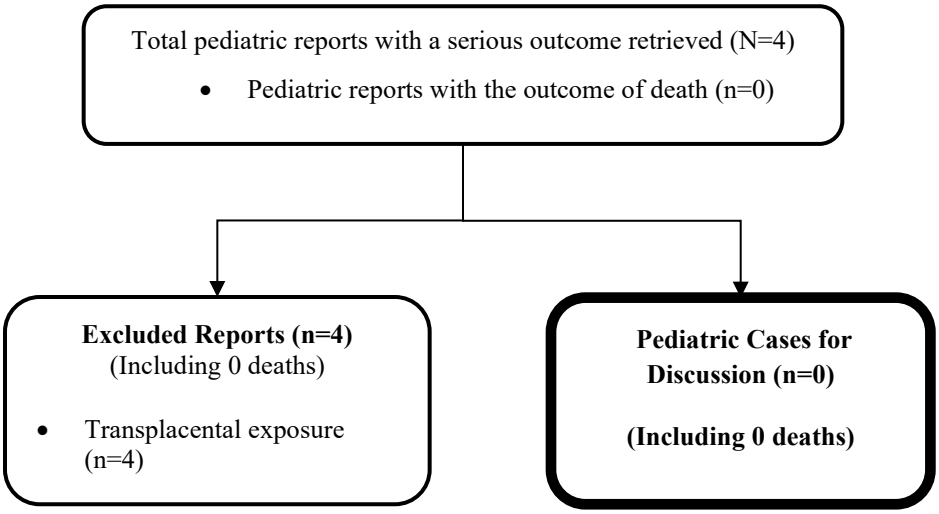
Table 3 presents the number of adult and pediatric FAERS reports from March 14, 2020, through October 10, 2024, with Triumeq and Triumeq PD.

Table 3. Total Adult and Pediatric FAERS Reports* Received by FDA From March 14, 2020, through October 10, 2024, With Triumeq and Triumeq PD			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	847 (558)	419 (132)	73 (35)
Pediatrics (0 - < 18 years)	17 (8)	13 (4)	0 (0)
* May include duplicates and transplacental exposures, and have not been assessed for causality † For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events. The coded outcomes are report-level outcomes, i.e., they reflect any serious outcomes for any adverse events coded to a Preferred Term in the FAERS report. Therefore, a serious outcome may not apply to all adverse events in a FAERS report. A review of the FAERS report narrative is necessary to determine adverse event-level outcomes and any association to a suspect product.			

3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved four U.S. serious pediatric reports for Triumeq from March 14, 2020, through October 10, 2024. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded four reports from the case series for the reasons listed in **Figure 1**, which presents the selection of cases for the pediatric case series.

Figure 1. Selection of U.S. Serious Pediatric Cases With Triumeq



3.1.3 Summary of U.S. Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.1.4 Summary of U.S. Serious Non-Fatal Pediatric Cases (N=0)

There are no non-fatal pediatric adverse event cases for discussion.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with Triumeq and Triumeq PD in pediatric patients less than 18 years of age from March 14, 2020, through October 10, 2024, and identified four reports with Triumeq; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with Triumeq and Triumeq PD in pediatric patients less than 18 years of age.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for Triumeq and Triumeq PD at this time and will continue routine pharmacovigilance monitoring.

6 REFERENCES

1. Triumeq and Triumeq PD (abacavir, dolutegravir, lamivudine) [package insert]. Research Triangle Park, NC: ViiV Healthcare; Revised June 2023.
2. Triumeq and Triumeq PD (abacavir, dolutegravir, lamivudine) [package insert]. Research Triangle Park, NC: ViiV Healthcare; Revised November 2017.
3. Triumeq and Triumeq PD (abacavir, dolutegravir, lamivudine) [package insert]. Research Triangle Park, NC: ViiV Healthcare; Revised March 2022.
4. Triumeq and Triumeq PD (abacavir, dolutegravir, lamivudine) [package insert]. Research Triangle Park, NC: ViiV Healthcare; Revised June 2024.
5. Chehab M, Kim I, Kapoor R, Diak IL. Triumeq Pediatric Postmarketing Pharmacovigilance Review. July 14, 2020. Available at: https://www.fda.gov/media/141748/download.
6. Brooks KM, Kiser JJ, Ziemba L, Ward S, Rani Y, Cressey TR, Masheto GR, Cassim H, Deville JG, Ponatshego, Patel F, Aurpibul L, Barnabas SL, Mustich I, Coletti A. Pharmacokinetics, safety, and tolerability of dispersible and immediate release abacavir/dolutegravir/lamivudine tablets in children with HIV (IMPAACT 2019): week 24 results of an open-label, multicenter, phase 1/2 dose confirmation study. Lancet HIV. 2023 Aug;10(8): e506-e517.

7 APPENDICES

7.1 APPENDIX A. 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 FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

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 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.