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

Pediatric Postmarketing Pharmacovigilance Review

Date:	October 25, 2023
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Product Name:	Truvada (emtricitabine; tenofovir disoproxil fumarate)
Pediatric Labeling Approval Date:	March 10, 2016
Application Type/Number:	NDA 021752
Applicant:	Gilead
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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Truvada (emtricitabine; tenofovir disoproxil fumarate) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). We focused on United States (U.S.) serious and unlabeled adverse events associated with Truvada in pediatric patients.

Truvada is a two-drug fixed dose combination product containing emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF). Both components of Truvada are Human Immunodeficiency Virus (HIV)-1 nucleoside analog reverse transcriptase inhibitors (NRTIs). Truvada was initially approved in the U.S. on August 2, 2004, and it is currently indicated for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 17 kg, in combination with other antiretroviral agents. In addition, Truvada is indicated for use in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP).

This pediatric postmarketing safety review was stimulated by the pediatric labeling on March 10, 2016, that expanded the Truvada indication from use in pediatric patients 12 years and older to use in pediatric patients weighing at least 17 kg who can swallow the tablet.

DPV reviewed all U.S. serious FAERS reports with Truvada in pediatric patients less than 18 years of age from September 30, 2016, through August 8, 2023, and we identified 134 reports; however, we excluded all reports 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 Truvada in pediatric patients less than 18 years of age.

DPV will continue routine pharmacovigilance monitoring for Truvada.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Truvada (emtricitabine; tenofovir disoproxil fumarate) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). We focused on United States (U.S.) serious and unlabeled adverse events associated with Truvada in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Truvada is a two-drug fixed dose combination product containing emtricitabine (Emtriva, FTC) and tenofovir disoproxil fumarate (Viread, TDF). Both components of Truvada are Human Immunodeficiency Virus (HIV)-1 nucleoside analog reverse transcriptase inhibitors (NRTIs). Truvada was initially approved in the U.S. on August 2, 2004, and it is currently indicated for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 17 kg, in combination with other antiretroviral agents. In addition, Truvada is indicated in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection.[1]

This pediatric postmarketing safety review was stimulated by the pediatric labeling on March 10, 2016, that expanded the Truvada indication from use in pediatric patients 12 years and older to use in pediatric patients weighing at least 17 kg who can swallow the tablet.[1,2] The recommended dosage in pediatric patients weighing at least 17 kg is one Truvada low-strength tablet (100mg/150mg, 133mg/200mg, or 167mg/250mg of FTC/TDF based on body weight) once daily taken orally with or without food.[1,2]

The Applicant did not conduct a pediatric trial to evaluate the safety and efficacy of the proposed Truvada low-strength tablets. The dosage recommendations were based on existing pharmacokinetics (PK), safety, and efficacy data from individual drug products that are approved for treatment of HIV infection in pediatric patients.[3]

On February 3, 2017, the Office of Surveillance and Epidemiology (OSE) completed a review of postmarketing adverse event reports with a serious outcome for Truvada in pediatric patients.[4] OSE's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with Truvada. On February 3, 2017, OSE's evaluation was presented to the Pediatric Advisory Committee (PAC) via web posting.

1.2 RELEVANT LABELED SAFETY INFORMATION[1]

The Truvada labeling contains the following safety information excerpted from the Highlights of Prescribing Information section and the *Pediatric Use* and *Clinical Trials in Pediatric Subjects* subsections. For additional Truvada labeling information, please refer to the full prescribing information.

BOXED WARNING:

- Severe acute exacerbations of hepatitis B (HBV) have been reported in HBV-infected individuals who have discontinued TRUVADA. Hepatic function should be monitored

closely in these individuals who discontinue TRUVADA. If appropriate anti-hepatitis B therapy may be warranted.

- TRUVADA used for HIV-1 PrEP must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiating and at least every 3 months during use. Drug-resistant HIV-1 variants have been identified with the use of TRUVADA for HIV-1 PrEP following undetected acute HIV-1 infection. Do not initiate TRUVADA for HIV-1 PrEP if signs or symptoms of acute HIV infection are present unless negative infection status is confirmed.

CONTRAINDICATIONS:

- TRUVADA for HIV-1 PrEP is contraindicated in individuals with unknown or positive HIV-1 status.

WARNINGS AND PRECAUTIONS:

- Comprehensive management to reduce the risk of acquiring HIV-1 when TRUVADA is used for HIV-1 PrEP: Use as part of a comprehensive prevention strategy including other prevention measures; strictly adhere to dosing schedule.
- Management to reduce the risk of acquiring HIV-1 drug resistance when TRUVADA is used for HIV-1 PrEP: refer to full prescribing information for additional detail.
- New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Avoid administering TRUVADA with concurrent or recent use of nephrotoxic drugs.
- Immune reconstitution syndrome during treatment of HIV-1 infection: may necessitate further evaluation and treatment.
- Decreases in bone mineral density (BMD): Consider assessment of BMD in individuals with a history of pathologic fracture or other risk factors for osteoporosis or bone loss.
- Lactic acidosis/severe hepatomegaly with steatosis: Discontinue TRUVADA in individuals who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity.

ADVERSE REACTIONS:

- In HIV-1 infected patients, the most common adverse reactions (incidence greater than or equal to 10%) are diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash.
- In HIV-1 uninfected adults in PrEP trials, adverse reactions that were reported by more than 2% of TRUVADA participants and more frequently than by placebo participants were headache, abdominal pain, and weight decreased.

Pediatric Use:

No pediatric clinical trial was conducted to evaluate the safety and efficacy of Truvada in patients with HIV-1 infection. Data from previously conducted trials with the individual drug products, FTC and TDF, were relied upon to support dosage recommendations for Truvada.

Clinical Trials in Pediatric Subjects:

- FTC (Emtriva): In addition to the adverse reactions reported in adults, anemia and hyperpigmentation were observed in 7% and 32%, respectively, of pediatric subjects (3

months to less than 18 years of age) who received treatment with FTC in the larger of two open-label, uncontrolled pediatric trials (N=116).

- TDF (Viread): In pediatric clinical trials (Studies 352 and 321) conducted in 184 HIV-1 infected subjects 2 to less than 18 years of age, the adverse reactions observed in pediatric subjects who received treatment with TDF were consistent with those observed in clinical trials of TDF in adults. In Study 352 (2 to less than 12 years of age), 89 pediatric subjects received TDF for a median exposure of 104 weeks. Of these, 4 subjects discontinued from the trial due to adverse reactions consistent with proximal renal tubulopathy. Three of these 4 subjects presented with hypophosphatemia and had decreases in total body or spine bone mineral density (BMD) Z-score. In Study 321 (12 to less than 18 years of age), the mean rate of BMD gain at Week 48 was less in the TDF compared to the placebo treatment group. Six TDF-treated subjects and one placebo-treated subject had significant (greater than 4%) lumbar spine BMD loss at Week 48. In both trials, skeletal growth (height) appeared to be unaffected.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 1**.

Table 1. FAERS Search Strategy*	
Date of search	August 9, 2023
Time period of search	September 30, 2016† - August 8, 2023
Search type	RxLogix Post-Market Cases
Product terms	Product Active Ingredients: emtricitabine\tenofovir, emtricitabine\tenofovir disoproxil, emtricitabine\tenofovir disoproxil fumarate
MedDRA search terms (Version 26.0)	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 Truvada ended on September 29, 2016. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports from September 30, 2016, through August 8, 2023, with Truvada.

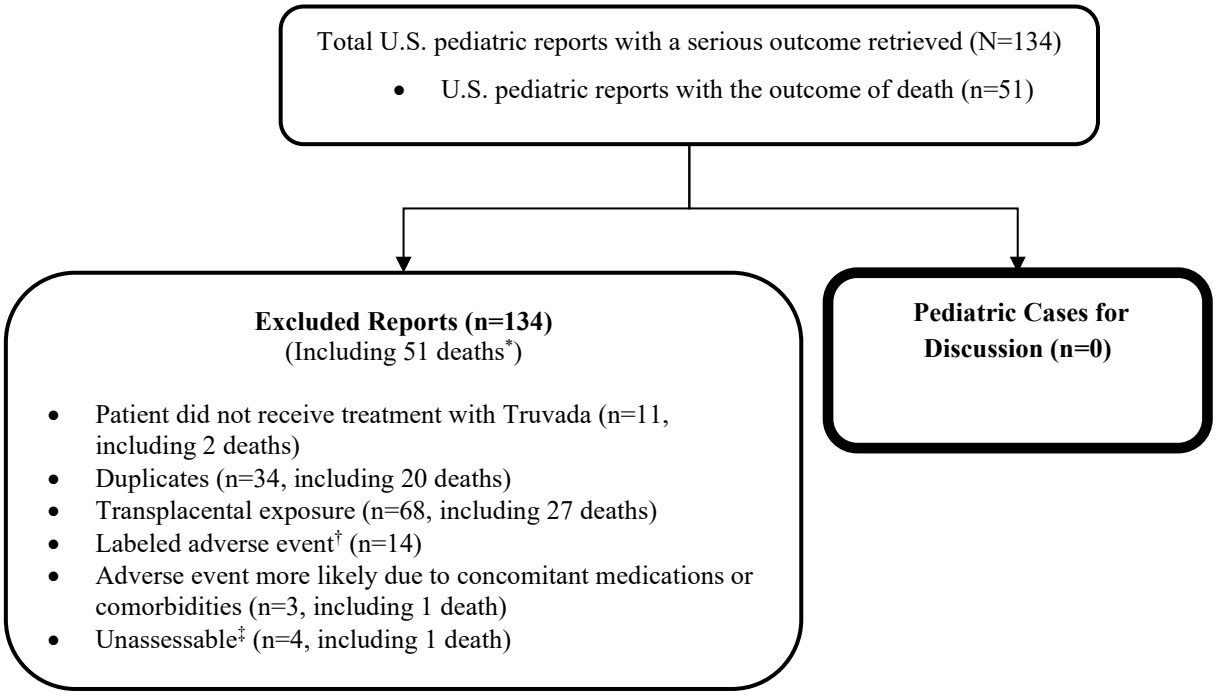
Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From September 30, 2016 through August 8, 2023, with Truvada			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	20,649 (17,027)	18,149 (14,580)	596 (387)
Pediatrics (0 - < 18 years)	555‡ (172)	515‡ (134)	105‡ (51)

* 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.
‡ This table includes thirty-two additional reports of U.S. pediatric deaths that were identified among reports not reporting an age. These reports are reflected in the counts of pediatric reports.

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

Our FAERS search retrieved 134 U.S. serious pediatric reports from September 30, 2016 through August 8, 2023. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded all reports from the case series for the reasons listed in Figure 1.

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



* Fifty-one excluded U.S. FAERS reports described fatal outcomes. None of the deaths were determined to be attributed to Truvada. These reports were excluded for the following reasons: the patient did not receive Truvada (n=2), report is a duplicate (n=20), the deaths occurred following transplacental exposure to Truvada (n=27). One case reported a patient who died due to chronic kidney disease, but the case had limited clinical information to understand the nature of the patient's renal disease and whether it was related to the patient's concurrent diseases, Truvada, or concomitant medications. Another case described a 12-year-old patient with acute lymphoblastic leukemia who died from graft-versus-host disease after umbilical cord blood transplantation. The patient's antiretroviral therapy with tenofovir\emtricitabine was discontinued before the transplant because the patient was not able to tolerate oral medications.

† Labeled adverse event does not represent increased severity or frequency.
‡ Unassessable: The report cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course, and outcome), the information is contradictory, or information provided in the report cannot be supplemented or verified.

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 Truvada in pediatric patients less than 18 years of age from September 30, 2016, through August 8, 2023, and we identified 134 reports; however, we excluded all reports 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 Truvada in pediatric patients less than 18 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Truvada (emtricitabine and tenofovir disoproxil fumarate) [product label]. Foster City, CA: Gilead Sciences Inc.; Revised June 2020. Accessed on August 8, 2023 at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021752s061lbl.pdf
2. Birnkrant D. Truvada, NDA 021752 Supplement 047 Approval Letter. March 10, 2016. Accessed on August 8, 2023 at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/021752Orig1s047ltr.pdf
3. Alacron A. Truvada Clinical Review. NDA 021752 Supplement 960. May 13, 2015. Accessed on August 8, 2023 at: https://www.fda.gov/media/97441/download
4. Gish P. Truvada Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review. February 2, 2017. Accessed on August 8, 2023 at: https://www.fda.gov/media/103210/download

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.

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