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:	February 15, 2024
Reviewers:	Vivian Dang, PharmD, Safety Evaluator Division of Pharmacovigilance (DPV)-II Ivone Kim, MD, Medical Officer DPV-I
Team Leader:	Rachna Kapoor, PharmD, MBA DPV-II
Deputy Division Director:	Ida-Lina Diak, PharmD, MS DPV-II
Product Name:	Tybost (cobicistat)
Pediatric Labeling Approval Dates:	August 22, 2019 and October 3, 2019
Application Type/Number:	NDA 203094
Applicant:	Gilead Sciences, Inc.
TTT Record ID:	2023-7605

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Tybost (cobicistat) 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). This review focuses on United States (U.S.) serious unlabeled adverse events associated with cobicistat in pediatric patients.

Cobicistat is a CYP3A inhibitor and was initially approved in the U.S. on September 24, 2014. Cobicistat is currently indicated for increase of systemic exposure of atazanavir or darunavir (once daily dosing regimen) in combination with other antiretroviral agents in the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and in pediatric patients weighing at least 35 kg co-administered with atazanavir or weighing at least 40 kg co-administered with darunavir.

This pediatric postmarketing safety review was stimulated by two pediatric labeling updates that expanded the cobicistat indication from use in adult patients to use in pediatric patients weighing at least 35 kg when co-administered with atazanavir on August 22, 2019, and use in pediatric patients weighing at least 40 kg when co-administered with darunavir on October 3, 2019.

DPV reviewed all U.S. serious FAERS reports with cobicistat in pediatric patients less than 18 years of age from September 24, 2014, through December 18, 2023, and 11 reports were identified; 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 cobicistat in pediatric patients less than 18 years of age.

DPV will continue routine pharmacovigilance monitoring for cobicistat.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Tybost (cobicistat) 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). This review focuses on United States (U.S.) serious unlabeled adverse events associated with cobicistat in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Cobicistat is a CYP3A inhibitor and was initially approved in the U.S. on September 24, 2014.[1] Cobicistat is currently indicated for increase of systemic exposure of atazanavir or darunavir (once daily dosing regimen) in combination with other antiretroviral agents in the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and in pediatric patients weighing at least 35 kg co-administered with atazanavir or weighing at least 40 kg co-administered with darunavir.[2]

This pediatric postmarketing safety review was stimulated by two pediatric labeling updates that expanded the cobicistat indication from use in adult patients to use in pediatric patients weighing at least 35 kg when co-administered with atazanavir on August 22, 2019, and use in pediatric patients weighing at least 40 kg when co-administered with darunavir on October 3, 2019.[3,4]

The safety of cobicistat was evaluated in HIV-1 infected virologically suppressed pediatric subjects between the ages of 12 to less than 18 years through Week 48 in an open-label clinical trial (Trial 128) of cobicistat co-administered with atazanavir (N=14) or darunavir (N=7) plus two nucleoside reverse transcriptase inhibitors. In this trial, the safety profile of cobicistat was similar to that in adults.[2,5,6]

A pediatric safety review for cobicistat has not previously been presented to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The cobicistat labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional cobicistat labeling information, please refer to the full prescribing information.[2]

CONTRAINDICATIONS:

- Coadministration with certain drugs for which altered plasma concentrations are associated with serious and/or life-threatening events or loss of therapeutic effect.

WARNINGS AND PRECAUTIONS:

- Assess creatinine clearance (CLcr) before initiating treatment.
- When TYBOST is used in combination with a tenofovir disoproxil fumarate (TDF)-containing regimen, cases of acute renal failure and Fanconi syndrome have been reported.

- Use with TDF: Assess urine glucose and urine protein at baseline and monitor CLcr, urine glucose, and urine protein. Monitor serum phosphorus in patients with or at risk for renal impairment.
- TYBOST in combination with more than one antiretroviral that requires pharmacokinetic enhancement (i.e., two protease inhibitors or elvitegravir in combination with a protease inhibitor) is not recommended.
- Use with HIV-1 protease inhibitors other than atazanavir or darunavir administered once daily is not recommended.
- Coadministration with drugs or regimens containing ritonavir is not recommended.

ADVERSE REACTIONS:
- The most common adverse drug reactions observed with TYBOST in combination with atazanavir (incidence greater than 5%, Grades 2−4) are jaundice and rash.

Pediatric Use:
- Use of TYBOST for this indication is supported by evidence from adequate and well-controlled studies in adults, and by pharmacokinetic, safety, and virologic data from an open-label trial (Trial 128) in virologically suppressed, HIV-1 infected pediatric subjects aged 12 years and older. The safety in these subjects through 48 weeks was similar to that in antiretroviral treatment-naïve adults.
- Safety and effectiveness of TYBOST in combination with atazanavir in pediatric patients weighing less than 35 kg have not been established. Safety and effectiveness of TYBOST in combination with darunavir in pediatric patients weighing less than 40 kg have not been established.

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	December 19, 2023
Time period of search	September 24, 2014† - December 18, 2023
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product Active Ingredient: Cobicistat
MedDRA search terms (Version 26.1)	All Preferred Terms
* See Appendix A for a description of the FAERS database. † U.S. approval date 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 24, 2014, through December 18, 2023, with cobicistat.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From September 24, 2014, Through December 18, 2023, With Cobicistat.

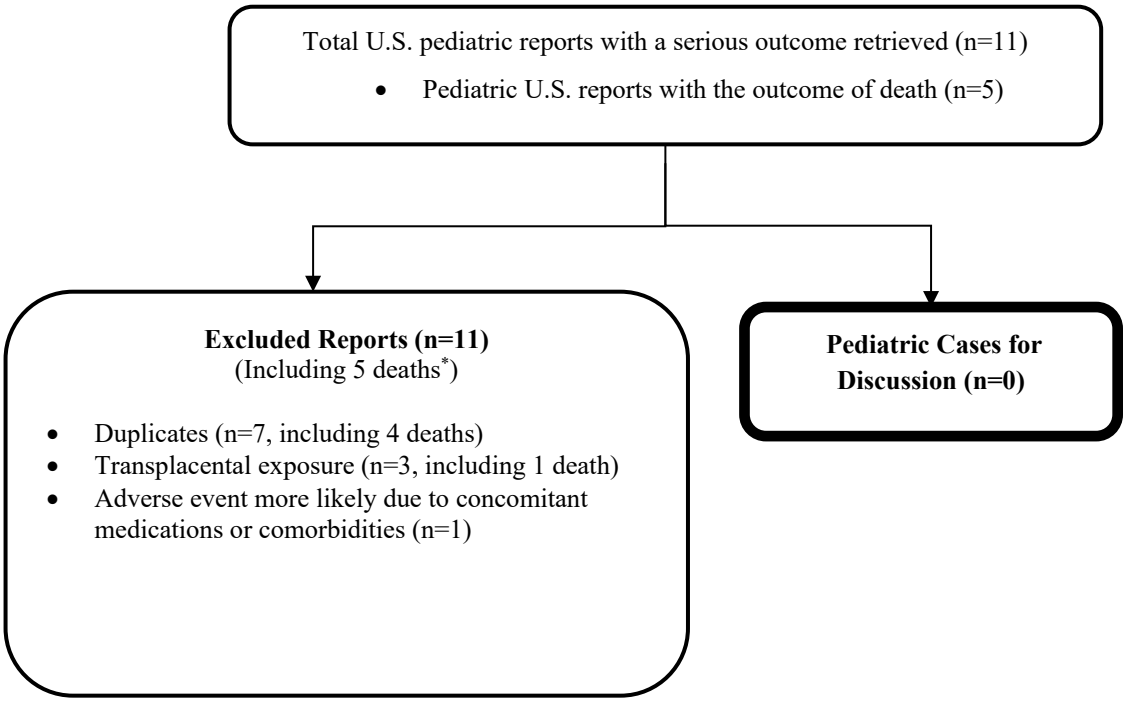
	All Reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 18 years)	194 (80)	176 (62)	14 (6)
Pediatrics (0 - < 18 years)	19‡ (11)	19‡ (11)	9‡ (5)

* 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 one additional report of pediatric death that was identified among U.S. reports not reporting an age. This report is reflected in the counts of pediatric reports.

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

Our FAERS search retrieved 11 U.S. serious pediatric reports from September 24, 2014, through December 18, 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 Cobicistat



* All excluded U.S. FAERS reports with a fatal outcome pertained to one unique case. This case described fetal death following an elective pregnancy termination.

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

There are no U.S. fatal pediatric adverse event cases for discussion.

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

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

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with cobicistat in pediatric patients less than 18 years of age from September 24, 2014, through December 18, 2023, and 11 reports were identified; 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 cobicistat in pediatric patients less than 18 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Birnkrant D. NDA 203094. Approval Letter. September 24, 2014. Accessed on December 19, 2023 at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/203094Orig2s000ltr.pdf

2. Tybost (cobicistat) [Package Insert]. Foster City, CA: Gilead Sciences.; Revised September 2021. Accessed on December 19, 2023 at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/203094s016lbl.pdf

3. Tybost (cobicistat) [Package Insert]. Foster City, CA: Gilead Sciences.; Revised August 2019. Accessed on December 19, 2023 at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/203094s013lbl.pdf

4. Tybost (cobicistat) [Package Insert]. Foster City, CA: Gilead Sciences.; Revised October 2019. Accessed on December 19, 2023 at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/203094s014lbl.pdf

5. Sampson M., Arya V. Tybost Clinical Pharmacology Review. NDA 203094 Supplement 13. August 2, 2019. Accessed on December 19, 2023 at: https://www.fda.gov/media/131618/download?attachment

6. Boyd S., Sherwat A. Tybost Clinical and Cross Discipline Team Leader Review. NDA 203094 Supplement 13. August 13, 2019. Accessed on December 19, 2023 at: https://www.fda.gov/media/131719/download?attachment

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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IDA-LINA DIAK
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