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:	May 7, 2025
Reviewers:	Brittany Patro, PharmD, BCPS, Safety Evaluator Division of Pharmacovigilance (DPV) II Ivone Kim, MD, Medical Officer DPV I
Team Leader:	Rachna Kapoor, PharmD, MBA DPV II
Associate Division Director:	Sara Camilli, PharmD, BCPS DPV II
Product Name:	Evotaz (atazanavir and cobicistat)
Pediatric Labeling Approval Date:	July 31, 2020
Application Type/Number:	NDA 206353
Applicant:	Bristol-Myers Squibb
TTT Record ID:	2025-14264

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Evotaz (atazanavir and 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 Evotaz in pediatric patients.

Evotaz is a two-drug combination of atazanavir, a human immunodeficiency virus (HIV-1) protease inhibitor, and cobicistat, a CYP3A inhibitor. Evotaz was initially approved in the U.S. on January 29, 2015, and is currently indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg.

This pediatric postmarketing safety review was prompted by the pediatric labeling on July 31, 2020, that expanded the Evotaz indication from use in adult patients to use in adults and pediatric patients weighing at least 35 kg.

DPV reviewed all U.S. serious FAERS reports with Evotaz in pediatric patients less than 18 years of age from January 29, 2015, through April 22, 2025, and identified five reports; however, all reports were excluded from further discussion as they all described transplacental exposure to Evotaz.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with Evotaz 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 Evotaz (atazanavir and cobicistat) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with Evotaz in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Evotaz is a two-drug combination of atazanavir, a human immunodeficiency virus (HIV-1) protease inhibitor, and cobicistat, a CYP3A inhibitor. Evotaz was initially approved in the U.S. on January 29, 2015, and is currently indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg.[1]

This pediatric postmarketing safety review was prompted by the pediatric labeling on July 31, 2020, that expanded the Evotaz indication from use in adult patients to use in adults and pediatric patients weighing at least 35 kg.[2]

No clinical trials with Evotaz as the fixed-dose tablet were performed in the pediatric population. The pharmacokinetics, safety, and efficacy of the components of Evotaz, atazanavir and cobicistat, were established in an open-label clinical trial GS-216-0128 in which 14 virologically suppressed HIV-1 pediatric participants aged 12 to less than 18 years, weighing at least 35 kg, received treatment with atazanavir, cobicistat, and two nucleotide reverse transcriptase inhibitors through Week 48.[1, 2]

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

1.2 RELEVANT LABELED SAFETY INFORMATION

The Evotaz labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional Evotaz labeling information, please refer to the full prescribing information.[1]

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

- EVOTAZ is contraindicated in patients with previously demonstrated hypersensitivity (e.g., Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of this product. (4)
- Coadministration with certain drugs for which altered plasma concentrations are associated with serious and/or life-threatening events or loss of therapeutic effect. (4)

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

- Cardiac conduction abnormalities: PR interval prolongation may occur in some patients. Consider ECG monitoring in patients with preexisting conduction system disease or when administered with other drugs that may prolong the PR interval. (5.1, 6, 7.3, 12.2, 17)
- Severe skin reactions: Discontinue if severe rash develops. (5.2, 6.1, 17)

- Assess creatinine clearance (CLcr) before initiating treatment. Consider alternative medications that do not require dosage adjustments in patients with renal impairment. (5.3)
- When cobicistat, a component of EVOTAZ, is used in combination with a tenofovir disoproxil fumarate (tenofovir DF)-containing regimen, cases of acute renal failure and Fanconi syndrome have been reported. (5.4)
- When used with tenofovir DF, 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. Coadministration with tenofovir DF is not recommended in patients with CLcr below 70 mL/min or in patients also receiving a nephrotoxic agent. (5.4)
- Chronic kidney disease has been reported during postmarketing surveillance in patients with HIV-1 infection treated with atazanavir, with or without ritonavir. Consider alternatives in patients at high risk for renal disease or with preexisting renal disease. Monitor renal laboratory tests prior to therapy and during treatment with EVOTAZ. Consider discontinuation of EVOTAZ in patients with progressive renal disease. (5.5)
- Nephrolithiasis and cholelithiasis have been reported. Consider temporary interruption or discontinuation. (5.6, 6)
- Hepatotoxicity: Patients with hepatitis B or C coinfection are at risk of increased transaminases or hepatic decompensation. Monitor hepatic laboratory tests prior to therapy and during treatment. (2.5, 5.7, 8.7)
- Antiretrovirals that are not recommended: EVOTAZ is not recommended for use with ritonavir or products containing ritonavir, or in combination with other antiretroviral drugs that require CYP3A inhibition to achieve adequate exposures (e.g., other protease inhibitors and elvitegravir). (5.9)
- Hyperbilirubinemia: Most patients experience asymptomatic increases in indirect bilirubin, which is reversible upon discontinuation. If a concomitant transaminase increase occurs, evaluate for alternative etiologies. (5.10, 6)
- Patients receiving EVOTAZ may develop immune reconstitution syndrome (5.11), new onset or exacerbations of diabetes mellitus/hyperglycemia (5.12, 6), and redistribution/accumulation of body fat (5.13).
- Hemophilia: Spontaneous bleeding may occur and additional factor VIII may be required. (5.14)

----------ADVERSE REACTIONS----------
Most common adverse reactions seen with atazanavir coadministered with cobicistat (greater than 5%, Grades 2-4) are jaundice and rash. (6.1)

----------USE IN SPECIFIC POPULATIONS----------
- Pediatrics: EVOTAZ is not recommended for patients weighing less than 35 kg. (8.4)

8.4 Pediatric Use

The safety and effectiveness of EVOTAZ for the treatment of HIV-1 infection in pediatric subjects weighing at least 35 kg was established through a study with components of EVOTAZ. Use of EVOTAZ 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 of components of EVOTAZ (Study GS-US-216-0128) in pediatric subjects with HIV-1 infection aged 12 years and older. The safety in these subjects through 48 weeks was similar to that in antiretroviral treatment-naive adults *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.2)]*.

Safety and effectiveness of EVOTAZ in the pediatric population weighing less than 35 kg have not been established. Atazanavir, a component of EVOTAZ, is not recommended for use in pediatric patients below the age of 3 months due to the risk of kernicterus.

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	April 23, 2025
Time period of search	January 29, 2015† - April 22, 2025
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product active ingredient: atazanavir sulfate\cobicistat, atazanavir\cobicistat
MedDRA search terms (Version 27.1)	All Preferred Terms
Other criteria	Case Seriousness: Serious‡ Country Derived: USA
* See Appendix A for a description of the FAERS database. † U.S. approval date ‡ 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. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, USA=United States of America	

3 RESULTS

3.1 FAERS

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

Our FAERS search retrieved five U.S. serious pediatric reports for patients less than 18 years old from January 29, 2015, through April 22, 2025.[a] We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded five reports from further discussion as they all described transplacental exposure to Evotaz.[b]

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

There are no fatal pediatric adverse event cases for discussion.

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

[a] Includes 1 pediatric report that was identified among reports not coded with an age.
[b] One report was coded with a fatal outcome. The report described a fetus conceived by a mother of advanced maternal age with asymptomatic HIV infection treated with dolutegravir, emtricitabine and tenofovir fumarate, and atazanavir sulfate and cobicistat. The fetus was diagnosed with trisomy 15. The pregnancy ended in fetal death but cause of death and other clinical details were not available.

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

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with Evotaz in pediatric patients less than 18 years of age from January 29, 2015, through April 22, 2025, and identified five reports; however, all reports were excluded from further discussion as they all described transplacental exposure to Evotaz.

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

5 CONCLUSION

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

6 REFERENCES

1. Evotaz (atazanavir and cobicistat) tablet [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. May 2023.
2. U.S. Food and Drug Administration. Supplemental NDA Approval Letter (S-7) for NDA 206353, Evotaz (atazanavir and cobicistat); tablet. July 31, 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/206353Orig1s007ltr.pdf.

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.