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 14, 2025
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Product Name:	Zerbaxa (ceftolozane and tazobactam)
Pediatric Labeling Approval Date:	April 21, 2022
Application Type/Number:	NDA 206829
Applicant:	Cubist Pharmaceutical, LLC
TTT Record ID:	2025-14549

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Zerbaxa (ceftolozane and tazobactam) 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 ceftolozane and tazobactam in pediatric patients.

Zerbaxa is a combination of ceftolozane, a cephalosporin antibacterial, and tazobactam, a beta-lactamase inhibitor, and was initially approved in the U.S. on December 19, 2014. Zerbaxa is currently indicated for treatment of the following infections caused by designated susceptible microorganisms:

- Complicated intra-abdominal infections, used in combination with metronidazole, in adult and pediatric patients (birth to less than 18 years of age)
- Complicated urinary tract infections, including pyelonephritis, in adult and pediatric patients (birth to less than 18 years of age)
- Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia in adult patients (18 years of age and older)

This pediatric postmarketing safety review was prompted by pediatric labeling on April 21, 2022, which expanded the indications for treatment of complicated intra-abdominal infections and complicated urinary tract infections from patients 18 years or older to also include pediatric patients from birth to less than 18 years of age.

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

DPV reviewed all U.S. serious FAERS reports with ceftolozane and tazobactam in pediatric patients less than 18 years of age from December 19, 2014, through May 5, 2025, and identified 12 reports; however, all reports were excluded from further discussion. Reports were excluded because of duplicate reporting (n=4), lack of an adverse event included in the report (n=3), insufficient details to meaningfully assess (n=3), report of an already adequately labeled event (n=1) and because the event more likely attributed to comorbidity (n=1).

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

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Zerbaxa (ceftolozane and tazobactam) 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 ceftolozane and tazobactam in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Zerbaxa is a combination of ceftolozane, a cephalosporin antibacterial, and tazobactam, a beta-lactamase inhibitor, and was initially approved in the U.S. on December 19, 2014.[1] Zerbaxa is currently indicated for treatment of the following infections caused by designated susceptible microorganisms:[1]

- Complicated intra-abdominal infections, used in combination with metronidazole, in adult and pediatric patients (birth to less than 18 years of age)
- Complicated urinary tract infections, including pyelonephritis, in adult and pediatric patients (birth to less than 18 years of age)
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This pediatric postmarketing safety review was prompted by pediatric labeling on April 21, 2022, which expanded the indications for treatment of complicated intra-abdominal infections and complicated urinary tract infections from patients 18 years or older to also include pediatric patients from birth to less than 18 years of age.[2]

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

1.2 RELEVANT LABELED SAFETY INFORMATION

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

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

• ZERBAXA is contraindicated in patients with known serious hypersensitivity to the components of ZERBAXA (ceftolozane and tazobactam), piperacillin/tazobactam, or other members of the beta-lactam class. (4)

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

• Decreased efficacy was observed in a Phase 3 cIAI trial in a subgroup of patients with baseline CrCl of 30 to 50 mL/min. Monitor CrCl at least daily in patients with changing renal function and adjust the dose of ZERBAXA accordingly. (5.1)
• Serious hypersensitivity (anaphylactic) reactions have been reported with beta-lactam antibacterial drugs. Exercise caution in patients with known hypersensitivity to beta-lactam antibacterial drugs. If an anaphylactic reaction to ZERBAXA occurs, discontinue the drug and institute appropriate therapy. (5.2)
• *Clostridioides difficile*-associated diarrhea (CDAD) has been reported with nearly all systemic antibacterial agents, including ZERBAXA. Evaluate if diarrhea occurs. (5.3)

---------- ADVERSE REACTIONS ----------
• Adult cIAI, cUTI and HAB/VABP Patients:
  o The most common adverse reactions in adult patients (≥5% in either the cIAI or cUTI indication) are nausea, diarrhea, headache, and pyrexia. (6.1).
  o The most common adverse reactions (≥5% in the HABP/VABP indication) are increase in hepatic transaminases, renal impairment/renal failure, and diarrhea. (6.1)
• Pediatric cIAI and cUTI Patients: The most common adverse reactions in pediatric patients (≥7% in either the cIAI or cUTI indication) are thrombocytosis, diarrhea, pyrexia, leukopenia, abdominal pain, vomiting, increased aspartate aminotransferase, and anemia. (6.1)

---------- USE IN SPECIFIC POPULATIONS ----------
• Pediatrics: Safety and effectiveness in pediatric patients with HABP/VABP have not been established. (8.4)

8.4 Pediatric Use

Complicated Intra-abdominal Infections (cIAI) and Complicated Urinary Tract Infections (cUTI), including Pyelonephritis

The safety and effectiveness of ZERBAXA for the treatment of cIAI and cUTI have been established in pediatric patients aged birth to less than 18 years old. Use of ZERBAXA in these age groups is supported by evidence from adequate and well-controlled studies of ZERBAXA in adults with cUTI and cIAI and additional pharmacokinetic and safety data from pediatric trials *[see Clinical Pharmacology (12.3) and Clinical Studies (14.1 and 14.2)]*.

The safety profile of ZERBAXA in pediatric patients was similar to adults with cIAI and cUTI, treated with ZERBAXA *[see Adverse Reactions (6.1)]*.

There is insufficient information to recommend dosage adjustment for pediatric patients younger than 18 years of age with cIAI and cUTI with eGFR 50 mL/min/1.73m^2 or less *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

ZERBAXA is not recommended in pediatric patients who have an eGFR 50 mL/min/1.73m^2 or less. Pediatric patients born at term or pre-term may not have an eGFR of 50 mL/min/1.73m^2 or greater at birth or within the first few months of life.

Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP)

The safety and effectiveness of ZERBAXA in pediatric patients have not been established for the treatment of HABP and VABP.

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	May 6, 2025
Time period of search	December 19, 2014[†] - May 5, 2025
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product active ingredient: ceftolozane sulfate\tazobactam sodium
MedDRA search terms (Version 28.0)	All Preferred Terms

Table 1. FAERS Search Strategy*	
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

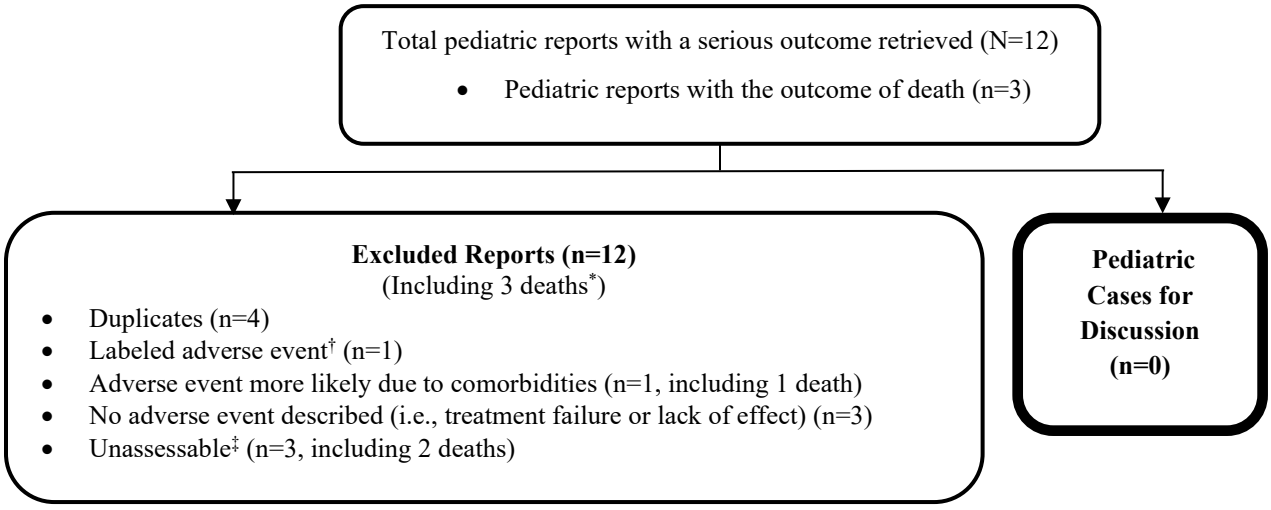
3 RESULTS

3.1 FAERS

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

Our FAERS search retrieved 12 U.S. serious pediatric reports for patients less than 18 years old from December 19, 2014, through May 5, 2025.[a] We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded all 12 reports from the case series for the reasons listed in **Figure 1**. **Figure 1** presents the selection of cases for the pediatric case series.

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



* Three excluded U.S. FAERS reports described fatal outcomes. None of the deaths could be attributed to ceftolozane and tazobactam. One death case described a patient who died from complications associated with recurrent bacteremia attributed to endovascular left ventricular assist device infection. Two death cases lacked sufficient clinical information to understand events that led to death or perform a causality assessment with ceftolozane and tazobactam.
† Labeled adverse event does not represent increased severity.
‡ Unassessable: The reports 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 reports cannot be supplemented or verified.

[a] Includes two pediatric reports that were identified among reports not coded with an age.

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)

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

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with ceftolozane and tazobactam in pediatric patients less than 18 years of age from December 19, 2014, through May 5, 2025, and identified 12 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 ceftolozane and tazobactam in pediatric patients less than 18 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Zerbaxa (ceftolozane and tazobactam) injection [package insert]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp, Cubist Pharmaceuticals, LLC. April 2022.
2. U.S. Food and Drug Administration. Supplemental NDA Approval Letter for NDA 206829 (S-011 and S-012), Zerbaxa (ceftolozane and tazobactam); injection. April 21, 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/206829Orig1s011,%20s012ltr.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.