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:	June 30, 2025
Reviewer:	Ivone Kim, MD Division of Pharmacovigilance I
Team Leader:	Carmen Cheng, PharmD Division of Pharmacovigilance I
Division Director:	Monica Muñoz, PharmD, PhD, BCPS Division of Pharmacovigilance I
Product Name:	Zosyn (piperacillin/tazobactam)
Pediatric Labeling Approval Date:	May 26, 2020
Application Type/Number:	NDA 050750/S-43, NDA 050684/S-96
Applicant:	Wyeth Pharmaceuticals, LLC.
TTT Record ID:	2025-14789

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EXECUTIVE SUMMARY

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

Zosyn is a combination of piperacillin, a penicillin-class antibacterial, and tazobactam, a beta-lactamase inhibitor. FDA initially approved Zosyn injection as powder for reconstitution (NDA 050684) on October 22, 1993. On February 24, 1998, FDA approved a new dosage form of Zosyn injection as solution in single-dose Galaxy containers (NDA 050750). Currently, Zosyn is approved for the treatment of:

- Intra-abdominal infections in adult and pediatric patients 2 months of age and older
- Nosocomial pneumonia in adult and pediatric patients 2 months of age and older
- Skin and skin structure infections in adults
- Female pelvic infections in adults
- Community-acquired pneumonia in adults

On July 26, 2006, the Zosyn labeling was updated to include available information on the use of Zosyn in pediatric patients aged 2 months or older with appendicitis and/or peritonitis.

On May 26, 2020, the Zosyn labeling was updated to reflect expansion of the use of Zosyn for the treatment of nosocomial pneumonia to include patients aged 2 months to <18 years.

This pediatric postmarketing safety review was prompted by pediatric labeling on May 26, 2020. A pediatric postmarketing pharmacovigilance review for piperacillin and tazobactam has not been previously presented to the Pediatric Advisory Committee.

DPV reviewed all U.S. serious FAERS reports with piperacillin and tazobactam in pediatric patients less than 18 years of age from October 22, 1993, to February 26, 2025, and identified 280 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 piperacillin and tazobactam in pediatric patients less than 18 years of age.

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

1 INTRODUCTION

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

1.1 PEDIATRIC REGULATORY HISTORY

Zosyn is a combination of piperacillin, a penicillin-class antibacterial, and tazobactam, a beta-lactamase inhibitor. FDA initially approved Zosyn injection as powder for reconstitution (NDA 050684)[a] on October 22, 1993.[1] On February 24, 1998, FDA approved a new dosage form of Zosyn injection as solution in single-dose Galaxy containers (NDA 050750).[3] Currently, Zosyn is approved for the treatment of:[4]

- Intra-abdominal infections in adult and pediatric patients 2 months of age and older
- Nosocomial pneumonia in adult and pediatric patients 2 months of age and older
- Skin and skin structure infections in adults
- Female pelvic infections in adults
- Community-acquired pneumonia in adults

On July 26, 2006, the Zosyn labeling was updated to include available information on the use of Zosyn in pediatric patients aged 2 months or older with appendicitis and/or peritonitis.[5,6]

On May 26, 2020, the Zosyn labeling was updated to reflect expansion of the use of Zosyn for the treatment of nosocomial pneumonia to include patients aged 2 months to <18 years.[7]

This pediatric postmarketing safety review was prompted by pediatric labeling on May 26, 2020. A pediatric postmarketing pharmacovigilance review for piperacillin and tazobactam has not been previously presented to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The Zosyn (piperacillin and tazobactam) injection for intravenous use labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional Zosyn labeling information, please refer to the full prescribing information.[4]

> **----------CONTRAINDICATIONS ----------**
>
> Patients with a history of allergic reactions to any of the penicillins, cephalosporins, or beta-lactamase inhibitors. (4)

[a] The Applicant for Zosyn discontinued NDA 050684 from market.[2] Zosyn remains available under NDA 050750.

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

- Serious hypersensitivity reactions (anaphylactic/anaphylactoid) reactions have been reported in patients receiving ZOSYN. Discontinue ZOSYN if a reaction occurs. (5.1)
- ZOSYN may cause severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis. Discontinue ZOSYN for progressive rashes. (5.2)
- Hemophagocytic lymphohistiocytosis (HLH) has been reported with the use of ZOSYN. If HLH is suspected, discontinue ZOSYN immediately. (5.3)
- Rhabdomyolysis: If signs or symptoms of rhabdomyolysis are observed, discontinue ZOSYN and initiate appropriate therapy. (5.4)
- Hematological effects (including bleeding, leukopenia and neutropenia) have occurred. Monitor hematologic tests during prolonged therapy. (5.5)
- As with other penicillins, ZOSYN may cause neuromuscular excitability or seizures. Patients receiving higher doses, especially in the presence of renal impairment may be at greater risk. Closely monitor patients with renal impairment or seizure disorders for signs and symptoms of neuromuscular excitability or seizures. (5.6)
- Nephrotoxicity in critically ill patients has been observed; the use of ZOSYN was found to be an independent risk factor for renal failure and was associated with delayed recovery of renal function as compared to other beta-lactam antibacterial drugs in a randomized, multicenter, controlled trial in critically ill patients. Based on this study, alternative treatment options should be considered in the critically ill population. If alternative treatment options are inadequate or unavailable, monitor renal function during treatment with ZOSYN. (5.7)
- *Clostridioides difficile*-associated diarrhea: evaluate patients if diarrhea occurs. (5.9)

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

The most common adverse reactions (incidence >5%) are diarrhea, constipation, nausea, headache, and insomnia. (6.1)

8.4 Pediatric Use

The safety and effectiveness of ZOSYN for intra-abdominal infections, and nosocomial pneumonia have been established in pediatric patients 2 months of age and older.

Use of ZOSYN in pediatric patients 2 months of age and older with intra-abdominal infections including appendicitis and/or peritonitis is supported by evidence from well-controlled studies and pharmacokinetic studies in adults and in pediatric patients. This includes a prospective, randomized, comparative, open-label clinical trial with 542 pediatric patients 2 to 12 years of age with intra-abdominal infections (including appendicitis and/or peritonitis), in which 273 pediatric patients received piperacillin and tazobactam [see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)].

Use of ZOSYN in pediatric patients 2 months of age and older with nosocomial pneumonia is supported by evidence from well-controlled studies in adults with nosocomial pneumonia, a simulation study performed with a population pharmacokinetic model, and a retrospective, cohort study of pediatric patients with nosocomial pneumonia in which 140 pediatric patients were treated with ZOSYN and 267 patients treated with comparators (which included ticarcillin-clavulanate, carbapenems, ceftazidime, cefepime, or ciprofloxacin) [see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)].

Because of the limitations of the available strengths and administration requirements (i.e., administration of fractional doses is not recommended) of ZOSYN Injection supplied in GALAXY Containers, and to avoid unintentional overdose, this product is not recommended for use if a dose of ZOSYN Injection in GALAXY Containers that does not equal 2.25 g, 3.375 g, or 4.5 g is required and an alternative formulation of ZOSYN should be considered [see Dosage and Administration (2.1, 2.5, and 2.6)].

The safety and effectiveness of ZOSYN have not been established in pediatric patients less than 2 months of age [see Clinical Pharmacology (12) and Dosage and Administration (2)].

Dosage of ZOSYN in pediatric patients with renal impairment has not been determined.

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	February 27, 2025
Time period of search	October 22, 1993† - February 26, 2025
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product active ingredient: piperacillin sodium\tazobactam sodium
MedDRA search terms (Version 27.1)	All Preferred Terms
Other search terms‡	Case Seriousness: Serious Country Derived: USA
* See Appendix A for a description of the FAERS database. † Zosyn initial FDA 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	

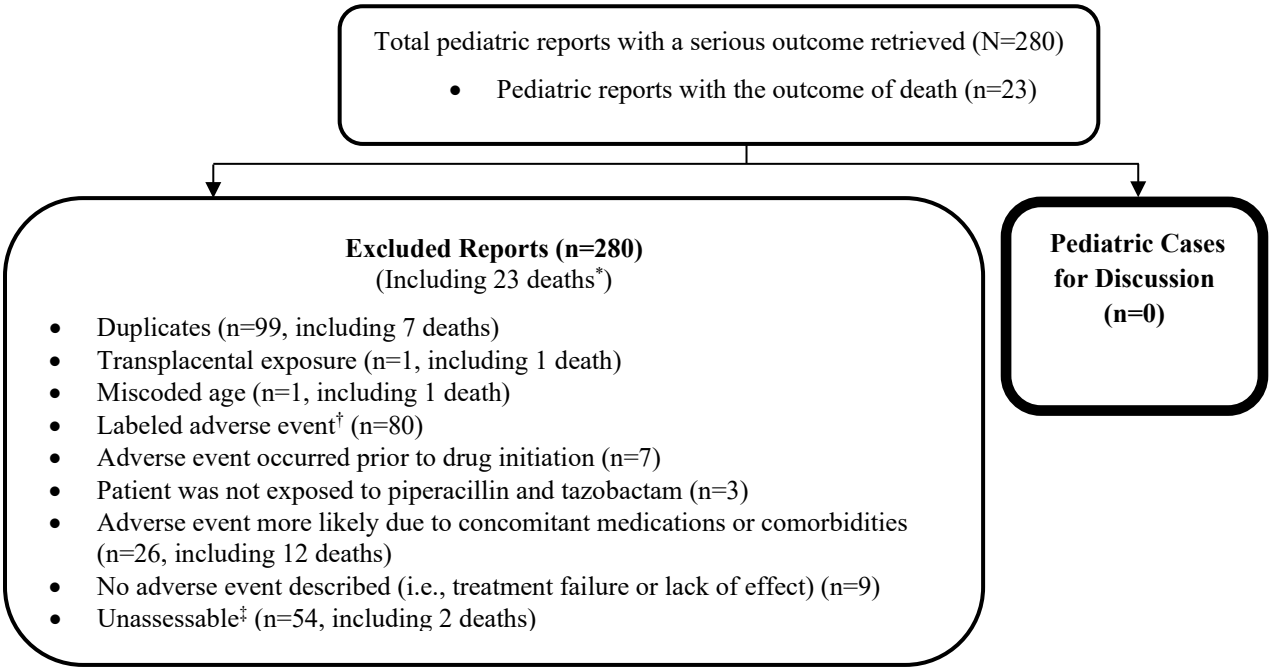
3 RESULTS

3.1 FAERS

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

Our FAERS search retrieved 280 U.S. serious pediatric reports for patients less than 18 years old from October 22, 1993 – February 26, 2025. We excluded all 280 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 Piperacillin and Tazobactam



* Twenty-three excluded U.S. FAERS reports described fatal outcomes. After accounting for duplicate reports (n=7) and reports describing adult patients miscoded as pediatric patients (n=1), we identified 15 unique cases describing fatal outcomes. None of the deaths were attributable to piperacillin and tazobactam. One case described fetal demise after prenatal exposure to chemotherapeutic agents and multiple medications during a pregnancy complicated by non-Hodgkin's lymphoma. Twelve cases described patients who died from other conditions including complications or progression of oncological disease (n=6), complications following surgeries for congenital heart diseases (n=3), complications from necrotizing enterocolitis in the setting of extreme prematurity (n=1), and complications from acute infections (vibrio vulnificus infection, n=1; parainfluenza with associated necrotizing pneumonia, n=1). Two cases reported fatal events but had insufficient clinical information to determine whether piperacillin and tazobactam may have been causally related to the death.

† Labeled adverse event does not represent increased severity.

‡ 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.

3.1.2 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 piperacillin and tazobactam in pediatric patients less than 18 years of age from October 22, 1993, to February 26, 2025, and identified 280 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 piperacillin and tazobactam in pediatric patients less than 18 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Zosyn (piperacillin and tazobactam for injection). NDA 050684. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=050684.
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5. Approval Letter. NDA 050750/S-014. July 26, 2006. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2006/050750s014LTR.pdf
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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.