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 20, 2024
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Product Name:	Teflaro® (ceftaroline fosamil) for injection
Pediatric Labeling Approval Date:	September 13, 2019
Application Type/Number:	NDA 200327
Applicant:	Allergan USA, Inc.
TTT Record ID:	2023-7560

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Teflaro® (ceftaroline fosamil) 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 ceftaroline fosamil in pediatric patients.

Teflaro® (ceftaroline fosamil) is a cephalosporin antibiotic, initially approved in the U.S. on October 29, 2010. Ceftaroline fosamil is currently indicated for the treatment of the following infections caused by susceptible bacteria: acute bacterial skin and skin structure infections (ABSSSI) in adult and pediatric patients at least 34 weeks gestational age and 12 days postnatal age, and community-acquired bacterial pneumonia (CABP) in adult and pediatric patients 2 months of age and older.

This pediatric postmarketing safety review was stimulated by the pediatric labeling on September 13, 2019, that expanded the use of ceftaroline fosamil for the treatment of ABSSSI in patients at least 34 weeks gestational age and 12 days postnatal age.

DPV reviewed all U.S. serious FAERS reports with ceftaroline fosamil in pediatric patients less than 18 years of age from March 6, 2018, through December 18, 2023, and identified five 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 ceftaroline fosamil in pediatric patients less than 18 years of age.

DPV will continue routine pharmacovigilance monitoring for ceftaroline fosamil.

Reference ID: 5331688

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Teflaro® (ceftaroline fosamil) 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 ceftaroline fosamil in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Teflaro® (ceftaroline fosamil) is a cephalosporin antibiotic that was initially approved in the U.S. on October 29, 2010. The original indications included the treatment of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP) caused by susceptible bacteria in patients ≥18 years of age.[1] The first pediatric approval was granted on May 27, 2016, for the same indications in pediatric patients 2 months of age and older.[2] On September 13, 2019, the indication for the treatment of ABSSSI was expanded to include pediatric patients of at least 34 weeks gestational age and 12 days postnatal age.[3]

The initial pediatric approval was based on Pediatric Efficacy Supplements submitted by the Applicant in December 2015, which established the safety and efficacy of ceftaroline fosamil in the treatment of ABSSSI and CABP in the age groups 2 months to less than 18 years.[4] Use of ceftaroline fosamil in these age groups was supported by evidence from adequate and well-controlled studies of ceftaroline fosamil in adults with additional pharmacokinetic and safety data from pediatric trials. Results from the clinical studies in pediatric patients showed that ceftaroline fosamil demonstrated a safety profile that was compatible with treatment of ABSSSI and CABP at the clinical dosages studied. In summary, the safety profile was similar to the safety profile seen in adults, and no safety concerns were identified beyond those already known to be cephalosporin class effects.

The subsequent pediatric approval for patients at least 34 weeks gestational age and 12 days postnatal age was based on a single study (NCT02424734) that enrolled 11 pediatric patients with a gestational age of at least 34 weeks and a postnatal age of 12 days to less than 2 months of age with known or suspected infections.[5] A finding of efficacy for this pediatric population was based on extrapolation from adult and older pediatric patients and pharmacokinetic model-based analyses demonstrating similar ceftaroline fosamil exposure in adults and the proposed pediatric population down to 34 weeks gestational age and 12 days postnatal age, using a dose of 6 mg/kg as a 30-to-60-minute infusion every 8 hours. Safety findings in these 11 patients were limited, but similar to those observed in adult and pediatric patients 2 months of age and older.

This pediatric postmarketing safety review was stimulated by the pediatric labeling update on September 13, 2019, that expanded the use of ceftaroline fosamil for the treatment of ABSSSI in pediatric patients of at least 34 weeks gestational age and 12 days postnatal age.

On April 30, 2018, DPV completed a pediatric postmarketing pharmacovigilance review for ceftaroline fosamil.[6] DPV's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with ceftaroline fosamil. On June 13, 2018, DPV's evaluation was presented to the Pediatric Advisory Committee via webposting.

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1.2 RELEVANT LABELED SAFETY INFORMATION

The ceftaroline fosamil labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection.[7] For additional ceftaroline fosamil labeling information, please refer to the full prescribing information.

----------CONTRAINDICATIONS----------
• Known serious hypersensitivity to ceftaroline or other members of the cephalosporin class. (4)

----------WARNINGS AND PRECAUTIONS----------
• Serious hypersensitivity (anaphylactic) reactions have been reported with beta-lactam antibacterial drugs, including Teflaro. If a hypersensitivity reaction occurs, discontinue Teflaro. (5.1)
• Clostridioides difficile-associated diarrhea (CDAD) has been reported with nearly all systemic antibacterial agents, including Teflaro. Evaluate if diarrhea occurs. (5.2)
• Neurological adverse reactions have been reported in patients treated with cephalosporins, including Teflaro. If neurological adverse reactions occur, consider discontinuing Teflaro or making appropriate dosage adjustments in patients with renal impairment. (2.3, 5.3)
• Direct Coombs' test seroconversion has been reported with Teflaro. If anemia develops during or after therapy, a diagnostic workup for drug induced hemolytic anemia should be performed and consideration given to discontinuation of Teflaro. (5.4)

----------ADVERSE REACTIONS----------
The most common adverse reactions occurring in >2% of adult patients and ≥3% of pediatric patients are diarrhea, nausea, and rash. Additional adverse reactions that occurred in ≥3% of pediatric patients include vomiting and pyrexia. (6.1)

8. USE IN SPECIFIC POPULATIONS

Pediatric Patients

The safety and effectiveness of Teflaro in the treatment of ABSSSI have been established in pediatric patients (at least 34 weeks gestational age and 12 days postnatal age). The safety and effectiveness of Teflaro in the treatment of CABP have been established in the age groups 2 months to less than 18 years old. Use of Teflaro in these age groups is supported by evidence from adequate and well-controlled studies of Teflaro in adults with additional pharmacokinetic and safety data in pediatric patients 2 months of age and older with ABSSSI or CABP [see Clinical Studies (14.1 and 14.2)]. Use of Teflaro in pediatric patients less than 2 months of age was supported by pharmacokinetic and safety data in 11 infants at least 34 weeks gestational age and 12 days postnatal age. In these infants, concentrations of Teflaro in the cerebrospinal fluid were not evaluated [see Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.2)]. Results from the clinical studies in pediatric patients show that Teflaro demonstrated a safety profile that was comparable with treatment of ABSSSI and CABP in adults at the clinical dosages studied.

Safety and effectiveness of Teflaro in pediatric patients less than 34 weeks gestational age and less than 12 days postnatal age for the treatment of ABSSSI have not been established.

Safety and effectiveness of Teflaro in pediatric patients below the age of 2 months for the treatment of CABP have not been established as no data are available.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

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

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Table 1. FAERS Search Strategy*	
Date of search	December 19, 2023
Time period of search	March 6, 2018† - December 18, 2023
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product active ingredient: ceftaroline, ceftaroline fosamil
MedDRA search terms (Version 26.1)	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 ceftaroline fosamil ended on March 5, 2018.
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 March 6, 2018 through December 18, 2023, with ceftaroline fosamil.

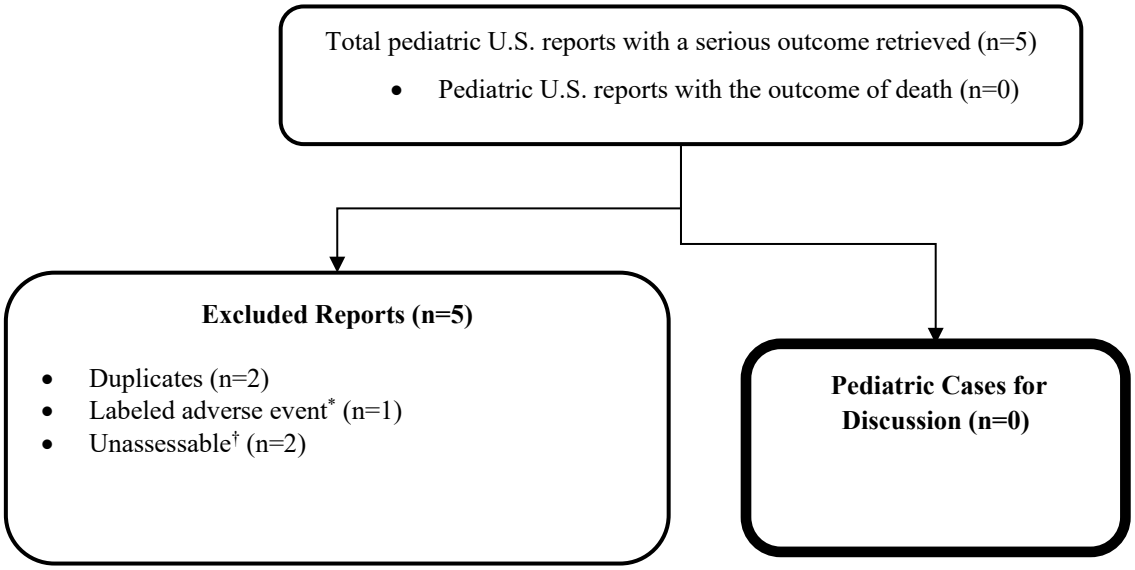
Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From March 6, 2018 through December 18, 2023, With Ceftaroline Fosamil			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	289 (136)	252 (106)	64 (24)
Pediatrics (0 - < 18 years)	12 (6)	11 (5)	1 (0)

* 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.

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

Our FAERS search retrieved five U.S. serious pediatric reports from March 6, 2018 through December 18, 2023. We reviewed all U.S. FAERS pediatric reports with a serious outcome and excluded all five reports from the case series for the reasons listed in Figure 1.

Figure 1. Selection of U.S. Serious Pediatric Cases With Ceftaroline Fosamil



* 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 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. serious non-fatal pediatric adverse event cases for discussion.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with ceftaroline fosamil in pediatric patients less than 18 years of age from March 6, 2018 through December 18, 2023, and five 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 ceftaroline fosamil in pediatric patients less than 18 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Food and Drug Administration. Approval Letter for NDA 200327, Teflaro (ceftaroline fosamil). October 29, 2010. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/200327Orig1s000Approv.pdf Accessed January 4, 2024.

2. Food and Drug Administration. Approval Letter for NDA 200327/S-16. May 27, 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/200327Orig1s016,s017ltr.pdf. Accessed January 4, 2024.

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4. Food and Drug Administration. Clinical and Cross-Discipline Team Leader Summary Review. NDA 200327 Supplement 16 and 17. May 25, 2016. Available at: https://www.fda.gov/files/drugs/published/N200327S0160---17-Ceftaroline-fosamil-Clinical-CD-PREA.pdf. Accessed January 4, 2024.

5. Food and Drug Administration. Clinical and Cross-Discipline Team Leader Summary Review. NDA 200327 Supplement 22. October 12, 2018. Available at: https://www.fda.gov/media/132146/download. Accessed January 4, 2024.

6. Wassel R, Cao K, Diak IL. Teflaro Pediatric Postmarketing Pharmacovigilance Review. April 30, 2018. Available at: https://www.fda.gov/media/113598/download. Accessed December 19, 2023.

7. Teflaro [package insert]. Madison, NJ: Allergan, USA, Inc. Revised October 2021.

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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