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Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

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Safety Evaluator: Ronald Wassel, PharmD
Division of Pharmacovigilance II (DPV II)

Team Leader: Kelly Cao, PharmD
DPV II

Deputy Division Director: Ida-Lina Diak, PharmD, MS
DPV II

Product Name: Teflaro® (ceftaroline fosamil) for injection

**Pediatric Labeling
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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome for Teflaro[®] (ceftaroline fosamil) for injection in pediatric patients.

Teflaro[®] was first approved in 2010 and is indicated in adult and pediatric patients 2 months of age and older for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP) caused by designated susceptible bacteria.

A review of the FDA Adverse Event Reporting System (FAERS) database identified no new safety signals, no increased severity or frequency of any labeled adverse events, and there were no deaths reported in the pediatric population with Teflaro[®].

There is no evidence from these data that there are new pediatric safety concerns with Teflaro[®] at this time.

We will continue to monitor adverse events associated with the use of Teflaro[®] for injection.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Teflaro® (ceftaroline fosamil) for injection is supplied as 600 mg or 400 mg of sterile ceftaroline fosamil powder in single-dose, 20 mL clear glass vials. The powder is constituted and further diluted for intravenous injection. It is indicated in adult and pediatric patients 2 months of age and older for the treatment of ABSSSI and CABP caused by designated susceptible bacteria.

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

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

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

-----CONTRAINDICATIONS-----

- Known serious hypersensitivity to ceftaroline or other members of the cephalosporin class.

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

- Serious hypersensitivity (anaphylactic) reactions have been reported with beta-lactam antibacterial drugs, including Teflaro. If a hypersensitivity reaction occurs, discontinue Teflaro.
- Clostridium difficile-associated diarrhea (CDAD) has been reported with nearly all systemic antibacterial agents, including Teflaro. Evaluate if diarrhea occurs.
- 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.

-----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.

2 POSTMARKET ADVERSE EVENT REPORTS

2.1 METHODS AND MATERIALS

2.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in Table 1. See Appendix A for a description of the FAERS database.

Table 1. FAERS Search Strategy

Date of Search	March 6, 2018
Time Period of Search	October 29, 2010* - March 5, 2018
Search Type	Mercado Quick Search Drug Safety Analytics
Product Names	Product Active Ingredient – Ceftaroline Ceftaroline fosamil
Search Parameters	All ages, all outcomes, worldwide

* U.S. Approval date

2.2 RESULTS

2.2.1 Total Number of FAERS Reports by Age

Table 2. Total Adult and Pediatric FAERS reports* from October 29, 2010, through March 5, 2018, with Teflaro® (ceftaroline fosamil) for injection

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	316 (241)	286 (212)	60 (24)
Pediatrics (0 - <17 years)	8 (8)	7 (7)	0 (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, and other serious important medical events.

2.2.2 Selection of Serious Pediatric Cases in FAERS

We identified seven pediatric reports with a serious outcome (See Table 2). After excluding duplicate reports, four cases remained.

2.2.3 Characteristics of Pediatric Case Series

Appendix B lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the Pediatric Case Series.

Table 3. Characteristics of Pediatric Case Series with Teflaro[®] (ceftaroline fosamil) for injection (N=4)

Age	12- < 17 years	4
Sex	Female	3
	Unknown	1
Country	United States	4
Reported Reason for Use	Cystic fibrosis-related pneumonia	3
	Methicillin-resistant Staphylococcal infection	1
Serious Outcome*	Hospitalization	1 [†]
	Required Intervention	1
	Other serious	4

* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events. Reports may have more than one outcome.

[†] Patient was already hospitalized; not related to the drug.

2.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=0)

There were no fatal pediatric adverse event cases.

2.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=4)

The reported events included hematologic toxicity (anemia, neutropenia, agranulocytosis), seizure (although no information such as diagnostic work up or treatment was provided, and ceftaroline was continued), and a hypersensitivity reaction manifested as hives. These events are included in the current label.

3 DISCUSSION

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events and there were no deaths reported in the pediatric population with Teflaro[®].

4 CONCLUSION

There is no evidence from these data that there are new pediatric safety concerns with Teflaro[®] at this time.

5 RECOMMENDATIONS

We will continue to monitor adverse events associated with the use of Teflaro[®].

6 APPENDICES

6.1 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 the FDA's postmarketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

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 or not 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.

6.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES WITH TEFLARO® (CEFTAROLINE FOSAMIL) FOR INJECTION (N=4)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	24-Dec-2014	10695518	1	1000067756	NON-EXPEDITED	12	Female	USA	OT
2	07-Dec-2015	11807231	1	US-FRI-1000080489	NON-EXPEDITED	14	Unknown	USA	OT
3	12-Aug-2016	12649519	1	US-TEVA-684183USA	EXPEDITED (15-DAY)	13	Female	USA	HO, OT
	16-Aug-2016	12654471 (duplicate)	1	US-NOVEL LABORATORIES, INC-2016-03557	EXPEDITED (15-DAY)				
	22-Feb-2018	14564176 (duplicate)	1	CH-ALLERGAN-1809415US	EXPEDITED (15-DAY)				
4	23-Jan-2018	14424949	1	US-MYLANLABS-2018M1005146	EXPEDITED (15-DAY)	12	Female	USA	OT
	01-Feb-2018	14474658 (duplicate)	1	US-TEVA-2018-US-853820	EXPEDITED (15-DAY)				

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. This outcome should not be confused with the clinical outcome of the reported adverse drug experience. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A report may have more than one serious outcome.
Abbreviations: HO=Hospitalization, OT=Other medically significant

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/s/

RONALD T WASSEL
04/30/2018

KELLY Y CAO
04/30/2018

IDA-LINA DIAK
04/30/2018