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Center for Drug Evaluation and Research
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Pediatric Postmarketing Pharmacovigilance Review

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Avycaz (ceftazidime/avibactam) in pediatric patients through age 17 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with ceftazidime/avibactam in pediatric patients.

FDA initially approved ceftazidime/avibactam for adult patients on February 25, 2015 and added two indications for pediatric patients 3 months or older on March 14, 2019. For pediatric patients, ceftazidime/avibactam is indicated for the treatment of complicated intra-abdominal infections (cIAI) in combination with metronidazole, as well as complicated urinary tract infections (cUTI) caused by susceptible Gram-negative organisms.

DPV reviewed all serious FAERS reports with ceftazidime/avibactam in the pediatric population (ages 0- <18 years) received by the FDA from February 25, 2015, through January 20, 2022. We evaluated 37 cases and did not identify any serious unlabeled adverse events associated with ceftazidime/avibactam.

DPV did not identify any new or unexpected pediatric safety signals with ceftazidime/avibactam and will continue to monitor for all adverse events associated with the use of ceftazidime/avibactam through routine pharmacovigilance.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Avycaz (ceftazidime/avibactam) in pediatric patients through age 17 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with ceftazidime/avibactam in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Ceftazidime/avibactam is an anti-infective combination product comprised of the semisynthetic cephalosporin ceftazidime and the non-beta-lactam beta-lactamase inhibitor avibactam for intravenous administration. FDA initially approved ceftazidime/avibactam for adult patients on February 25, 2015,[1] and added two indications for pediatric patients 3 months or older on March 14, 2019.[2] For pediatric patients 3 months and older, ceftazidime/avibactam in combination with metronidazole is indicated for the treatment of complicated intra-abdominal infections (cIAI) caused by the following susceptible Gram-negative organisms: *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Enterobacter cloacae, Klebsiella oxytoca, Citrobacter freundii* complex, and *Pseudomonas aeruginosa*. Additionally, it is indicated for the treatment of complicated urinary tract infections (cUTI) including pyelonephritis caused by the following susceptible Gram-negative organisms: *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Citrobacter freundii* complex, *Proteus mirabilis*, and *Pseudomonas aeruginosa*. Notably, on February 1, 2018, ceftazidime/avibactam was approved for hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) among adult patients.[3]

Support for the approval of ceftazidime/avibactam for pediatric patients for the treatment of cIAI and cUTI came from two, phase 2, single-blinded, randomized, multicenter active-controlled trials.[4] Study D4280C00015 (NCT02475733) compared ceftazidime/avibactam in combination with metronidazole to meropenem for the treatment of cIAI, while study D4280C00016 (NCT02497781) compared ceftazidime/avibactam to cefepime for the treatment of cUTI. The primary endpoint in these trials was to establish safety and tolerability of ceftazidime/avibactam in the pediatric patient population 3 months or older. These trials also evaluated pharmacokinetics (PK) as well as descriptive efficacy as the trials were not designed for inferential efficacy testing. Instead, efficacy was extrapolated from the adult trials as the studied disease courses are similar between the adult and pediatric populations. Therefore, the studies were designed with a relatively small sample size. Patients were randomized 3:1 to receive ceftazidime/avibactam or comparator (i.e., meropenem or cefepime). Cumulatively, 128 pediatric patients were exposed to ceftazidime/avibactam between these two trials with 61 patients in the cIAI trial and 67 patients in the cUTI trial. No deaths were observed. Treatment was discontinued due to adverse reactions in 2.3% (3/128) of patients receiving ceftazidime/avibactam and 0/50 of patients receiving comparator drugs. The safety profile of ceftazidime/avibactam in pediatric patients was similar to that of adult patients, with the most common adverse reactions being vomiting, diarrhea, rash, and infusion site phlebitis.[5] These safety findings are consistent with published medical literature evaluating ceftazidime/avibactam for the treatment of cUTI and cIAI in the pediatric patient population.[6,7]

Reference ID: 5036015

This review was triggered by the approval for ceftazidime/avibactam use in pediatric patients 3 months and older on March 14, 2019. DPV has not previously presented ceftazidime/avibactam to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The Avycaz (ceftazidime/avibactam) labeling provides the following safety information (excerpted from the pertinent sections).[5] For further ceftazidime/avibactam labeling information, please refer to the full prescribing information.

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

AVYCAZ is contraindicated in patients with known serious hypersensitivity to the components of AVYCAZ (ceftazidime and avibactam), avibactam-containing products or other members of the cephalosporin class.

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

- Decreased efficacy in adult cIAI patients with baseline CrCl of 30 to less than or equal to 50 mL/ min: Monitor CrCl at least daily in adult and pediatric patients with changing renal function and adjust the dose of AVYCAZ accordingly. (5.1)
- Hypersensitivity reactions: Includes anaphylaxis and serious skin reactions. Cross-hypersensitivity may occur in patients with a history of penicillin allergy. If an allergic reaction occurs, discontinue AVYCAZ. (5.2)
- Clostridium difficile-associated diarrhea (CDAD): CDAD has been reported with nearly all systemic antibacterial agents, including AVYCAZ. Evaluate if diarrhea occurs. (5.3)
- Central Nervous System Reactions: Seizures and other neurologic events may occur, especially in patients with renal impairment. Adjust dose in patients with renal impairment. (5.4)

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

- Adult cIAI, cUTI and HABP/VABP Patients: The most common adverse reactions in cIAI (≥ 5%, when used with metronidazole) patients are diarrhea, nausea and vomiting. The most common adverse reactions (3%) in cUTI patients are diarrhea and nausea. The most common adverse reactions (≥ 5%) in HABP/VABP patients were diarrhea and vomiting. (6.1)
- Pediatric cIAI and cUTI Patients: The most common adverse reactions (> 3%) in pediatric patients were vomiting, diarrhea, rash, and infusion site phlebitis. (6.1)

USE IN SPECIFIC POPULATIONS

- Safety and effectiveness in pediatric patients below the age of 3 months have not been established. (8.4)
- Safety and effectiveness in pediatric patients with HABP/VABP have not been established. (8.4)

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

Reference ID: 5036015

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

Table 1. FAERS Search Strategy*	
Date of search	March 9, 2022
Time period of search	February 25, 2015† - January 20, 2022
Search type	*Quick Query*
Product terms	Product active ingredient: avibactam sodium\ceftazidime Product name: Avycaz
MedDRA search terms (Version 24.1)	All PT terms
* See **Appendix A** for a description of the FAERS database. † U.S. approval date Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term	

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 February 25, 2015 - January 20, 2022, with ceftazidime/avibactam.

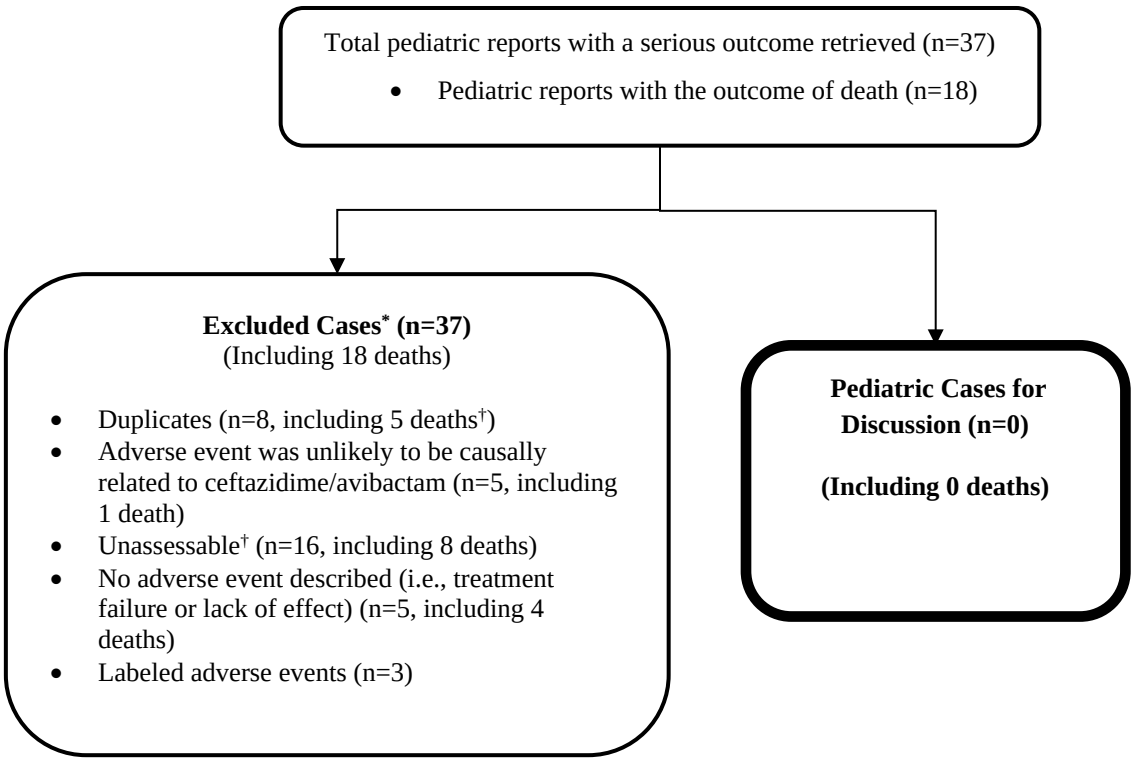
Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From February 25, 2015 - January 20, 2022, with Avycaz (ceftazidime/avibactam)			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	498 (65)	477 (51)	186 (17)
Pediatrics (0 - <18 years)	48 (5)	37‡ (2)	18‡ (1)
* 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. ‡ See **Figure 1**. Three reports of pediatric death were identified among reports not reporting an age. These reports are reflected in the counts of pediatric reports.			

3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved 37 serious pediatric reports from February 25, 2015 - January 20, 2022. We reviewed all FAERS pediatric reports with a serious outcome and did not identify any serious unlabeled adverse events associated with ceftazidime/avibactam (see **Figure 1**).

Figure 1 presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious Pediatric Cases with Avycaz (ceftazidime/avibactam)



* DPV reviewed these cases, but they were excluded from further discussion for the reasons listed above

† Of the 18 death reports identified, 5 were duplicate reports. Among the 13 unique cases, the relationship between death and ceftazidime/avibactam use was unassessable in most cases, more likely related to the infection (e.g., patient critically ill prior to drug initiation), or related to an alternative co-morbid condition (e.g., fungal infection, cancer).

† Unassessable: Case 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) or the information is contradictory, or information provided in the case cannot be supplemented or verified.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for further discussion.

3.1.4 Summary of Non-Fatal Pediatric Serious Adverse Event Cases (N=0)

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

4 DISCUSSION

DPV reviewed all 37 serious FAERS reports with ceftazidime/avibactam in the pediatric population (ages 0-<18 years) received by FDA from February 25, 2015, through January 20,

2022. We excluded all reports from the case series. We identified no new safety signals, no increased severity or frequency of any labeled adverse events and there were no deaths directly associated with ceftazidime/avibactam.

5 CONCLUSION

DPV did not identify any pediatric safety concerns for ceftazidime/avibactam at this time.

6 RECOMMENDATION

DPV will continue to monitor all adverse events associated with the use of ceftazidime/avibactam through routine pharmacovigilance.

7 REFERENCES

[1] Avycaz (ceftazidime/avibactam) [package insert]. Madison, NJ: Allergen USA, Inc. February 25, 2015. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206494s000lbl.pdf. Accessed on June 24, 2022.

[2] Avycaz (ceftazidime/avibactam) [package insert]. Madison, NJ: Allergen USA, Inc. Revised March 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/206494s005,s006lbl.pdf. Accessed on June 24, 2022.

[3] Avycaz (ceftazidime/avibactam) [package insert]. Madison, NJ: Allergen USA, Inc. Revised February 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/206494s004lbl.pdf. Accessed on June 24, 2022.

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[5] Avycaz (ceftazidime/avibactam) [package insert]. Madison, NJ: Allergen USA, Inc. Revised November 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/206494s007lbl.pdf. Accessed on June 24, 2022.

[6] Bradley JS, Broadhurst H, Cheng K, Mendez M, Newell P, Prchlik M, Stone GG, Talley AK, Tawadrous M, Wajsbrot D, Yates K, Zuzova A, Gardner A. Safety and Efficacy of Ceftazidime-Avibactam Plus Metronidazole in the Treatment of Children ≥3 Months to <18 Years With Complicated Intra-Abdominal Infection: Results From a Phase 2, Randomized, Controlled Trial. Pediatr Infect Dis J. 2019 Aug;38(8):816-824. doi: 10.1097/INF.0000000000002392. PMID: 31306396.

[7] Bradley JS, Roilides E, Broadhurst H, Cheng K, Huang LM, MasCasullo V, Newell P, Stone GG, Tawadrous M, Wajsbrot D, Yates K, Gardner A. Safety and Efficacy of Ceftazidime-Avibactam in the Treatment of Children ≥3 Months to <18 Years With Complicated Urinary Tract Infection: Results from a Phase 2 Randomized, Controlled Trial. Pediatr Infect Dis J. 2019 Sep;38(9):920-928. doi: 10.1097/INF.0000000000002395. PMID: 31335570.

8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

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 (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.

Reference ID: 5036015

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