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:	August 29, 2023
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Product Name:	Dificid (fidaxomicin)
Pediatric Labeling Approval Date:	January 24, 2020
Application Type/Numbers:	NDA 201699, NDA 213138
Applicant:	Cubist Pharmaceuticals LLC
TTT Record ID:	2023-5019

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Dificid (fidaxomicin) in pediatric patients younger than age 18 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA). This review focuses on serious unlabeled adverse events associated with fidaxomicin in pediatric patients.

The FDA approved fidaxomicin on May 27, 2011, for the treatment of *Clostridium difficile*-associated diarrhea (CDAD) in adults (≥ 18 years of age). On January 24, 2020, the indication was expanded to include pediatric patients 6 months of age and older.

DPV reviewed all serious FAERS reports with fidaxomicin in the pediatric population (ages 0 - < 18 years) received by FDA from May 27, 2011, through June 5, 2023, and identified one case for inclusion in our case series. The case reported the adverse event of hallucinations and while the case described a temporal association with fidaxomicin and a positive dechallenge, other possible causes of hallucinations could not be ruled out. There was insufficient evidence to support a signal of hallucinations with fidaxomicin at this time. In our review of serious adverse events with fidaxomicin in the pediatric population, we did not identify any new safety signals or an increased severity or frequency of labeled adverse events and there were no deaths.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Dificid (fidaxomicin) in pediatric patients younger than age 18 years. DPV conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA). This review focuses on serious unlabeled adverse events associated with fidaxomicin in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Fidaxomicin is a macrolide antibacterial indicated for the treatment of *C. difficile*-associated diarrhea (CDAD). FDA approved fidaxomicin as tablets for adults (≥ 18 years of age) on May 27, 2011.[1] On January 24, 2020, the indication was expanded to include pediatric patients 6 months of age and older.[2] On this same date, an oral suspension of fidaxomicin was also approved.

Support for the approval of the pediatric indication came from SUNSHINE (28190CL-0202), a phase 3, multicenter, investigator-blind, randomized, parallel group study comparing the safety and efficacy of fidaxomicin and vancomycin in pediatric patients with CDAD.[3] Eligible patients were aged from birth (6 months in the United States) to < 18 years of age with a diagnosis of CDAD. Patients were randomized in a 2:1 ratio to either fidaxomicin or vancomycin with 98 patients receiving fidaxomicin and 44 receiving vancomycin. Fidaxomicin provided comparable rates of confirmed clinical response, which was defined as resolution of diarrhea in addition to not needing CDAD treatment for 2 days after the end of 10 days of treatment. A lower confirmed clinical response rate was seen in patients < 2 years in the fidaxomicin arm compared to the vancomycin arm, however, the interpretation of this finding was felt to be confounded by the small number of patients treated and by difficulties diagnosing CDAD in children < 2 years. Sustained clinical response, defined as confirmed clinical response and no CDAD recurrence through 30 days after the end of treatment, was higher for fidaxomicin than for vancomycin.

Safety was primarily evaluated by the SUNSHINE study but was also supported by OPT-80-206, a phase 2a, open-label, uncontrolled, safety, tolerability, and PK study in pediatric patients with CDAD. From these studies, a total of 136 patients aged 1 month to 18 years were treated with fidaxomicin. The most frequent adverse reactions in fidaxomicin-treated patients included pyrexia, headache, vomiting, diarrhea, abdominal pain, constipation, and increased aminotransferases. Four deaths occurred in fidaxomicin-treated patients, including 1 death in study OPT-80-206 and 3 deaths in the SUNSHINE study, whereas no deaths were reported in the vancomycin arm in the SUNSHINE study during the study period. All of the patients who died were less than 2 years of age. The deaths were assessed to be related to underlying comorbid illnesses (e.g., hematological malignancies, concomitant chemotherapy, complications of hematopoietic stem cell transplantation). No fidaxomicin-related toxicities were identified that could have resulted in the fatal outcomes.

This pediatric postmarketing pharmacovigilance review was prompted by the approval in pediatric patients on January 24, 2020. DPV has not previously presented fidaxomicin to the Pediatric Advisory Committee.

Fidaxomicin is available as tablets and an oral suspension. Pediatric dosing of the oral tablets is for patients weighing at least 12.5 kg and is one 200 mg tablet orally twice a day for 10 days.[4] Pediatric dosing of the oral suspension is for patients weighing at least 4 kg and is weight-based dosing twice daily for 10 days.

1.2 RELEVANT LABELED SAFETY INFORMATION

The fidaxomicin labeling provides the following safety information (excerpted from the pertinent sections). For further fidaxomicin labeling information, please refer to full prescribing information.[4]

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

DIFICID is contraindicated in patients who have known hypersensitivity to fidaxomicin or any other ingredient in DIFICID. (4)

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

- Acute hypersensitivity reactions (angioedema, dyspnea, pruritus, and rash) have been reported. If a severe hypersensitivity reaction occurs, discontinue DIFICID. (5.1)
- DIFICID is not expected to be effective for the treatment of other types of infections due to minimal systemic absorption of fidaxomicin. DIFICID should only be used for the treatment of C. difficile-associated diarrhea. (5.2)
- Development of drug-resistant bacteria: Only use DIFICID for infection proven or strongly suspected to be caused by C. difficile. (5.3)

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

The most common adverse reactions in adults (incidence ≥2%) are nausea, vomiting, abdominal pain, gastrointestinal hemorrhage, anemia, and neutropenia. (6)

The most common adverse reactions in pediatric patients (incidence ≥5%) treated with DIFICID are pyrexia, abdominal pain, vomiting, diarrhea, constipation, increased aminotransferases, and rash. (6)

----------USE IN SPECIFIC POPULATIONS ----------

Pediatric Use

The safety and effectiveness of DIFICID for the treatment of CDAD have been established in pediatric patients 6 months to less than 18 years of age. Use of DIFICID in these age groups is supported by evidence from adequate and well-controlled trials of DIFICID in adults with CDAD and pharmacokinetic, safety and efficacy data from pediatric trials [see Clinical Pharmacology (12.3), Clinical Studies (14.2)]. No new safety signals associated with the use of DIFICID in pediatric patients were identified in the pediatric trials [see Adverse Reactions (6.1)].

The safety and effectiveness of DIFICID have not been established in pediatric patients younger than 6 months of age.

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	June 6, 2023
Time period of search	May 27, 2011† - June 5, 2023
Search type	RxLogix PV Reports Quick Query
Product terms	Product Active Ingredient (PAI): Fidaxomicin
MedDRA search terms (Version 26.0)	All PTs
* See Appendix A for a description of the FAERS database. † U.S. approval date for fidaxomicin 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 May 27, 2011, through June 5, 2023 with fidaxomicin.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From May 27, 2011 through June 5, 2023 With Fidaxomicin			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	962 (571)	636 (253)	151 (38)
Pediatrics (0 - <18 years)	19 (15)	8 (4)	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, or other serious important medical events.			

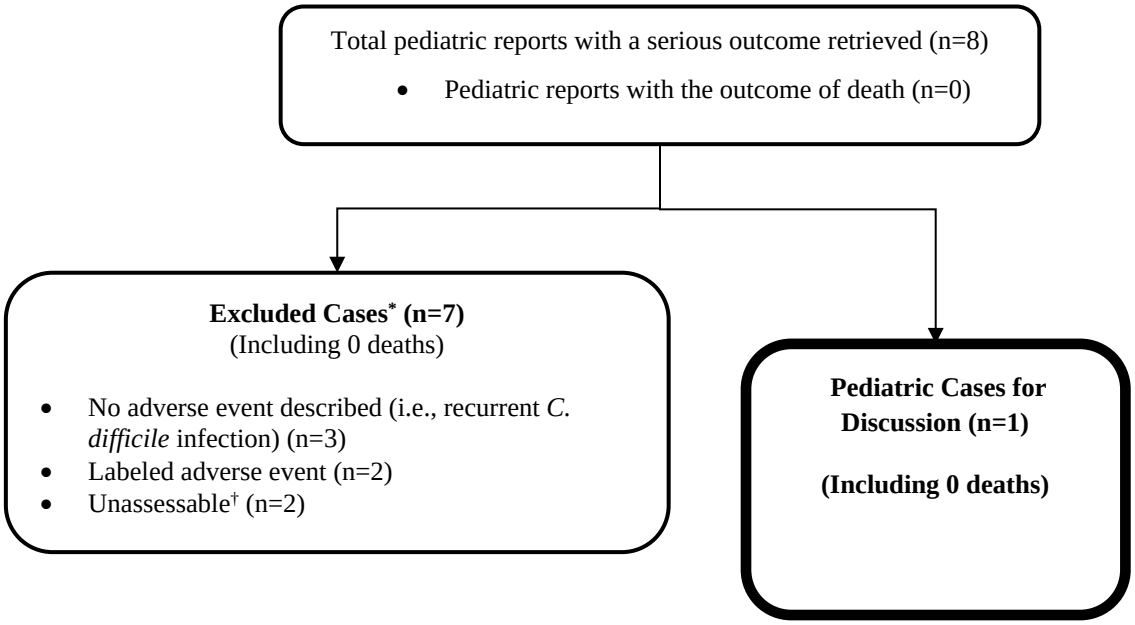
3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved eight serious pediatric reports from May 27, 2011, through June 5, 2023.

We reviewed all FAERS pediatric reports with a serious outcome. We excluded reports from the case series for various reasons, such as if there was no adverse event described (n=3; recurrent *C. difficile* infection), if the report described a labeled adverse event (n=2), or if the report was unassessable due to limited information (n=2). We summarize the remaining case in section 3.1.4 below.

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

Figure 1. Selection of Serious Pediatric Cases with Fidaxomicin



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

† 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)

We did not identify any fatal pediatric adverse event reports associated with fidaxomicin.

3.1.4 Summary of Non-Fatal Pediatric Serious Cases (N=1)

We identified one serious FAERS case with fidaxomicin in the pediatric population reporting a non-fatal serious outcome. The case reported hallucinations and this case is summarized below:

FAERS Case #20951191, United States, Initial FDA Received Date: June 10, 2022, Direct Report, Serious Outcome: Other Serious[a]

A 3-year-old female with a past medical history of recurrent *C. difficile* infection (treated previously with vancomycin including an extended course with a slow taper), chronic

[a] Case summary includes information from duplicate version of case: FAERS Case #21141808, United States, Initial FDA Received Date: July 27, 2022, Direct Report

constipation, and gastroesophageal reflux disease was treated with fidaxomicin for another recurrence of *C. difficile* infection. She reportedly was responding to the fidaxomicin with resolution of her diarrhea, however, five days after starting the fidaxomicin, the patient experienced "severe visual hallucinations." It was reported that "she woke up and thought there were snakes in her bed." These symptoms lasted for eight hours and required an emergency room visit. After discontinuation of fidaxomicin, the hallucinations stopped and did not recur.

Reviewers' Comments: The temporal relationship and positive dechallenge support an association between the hallucinations and fidaxomicin administration. Underlying infection was considered as a possible cause, however, the patient's C. difficile *symptoms were reportedly improving. Concomitant medications cannot be ruled out as a potential contributing factor as no concomitant medications were reported in the case.*

4 DISCUSSION

DPV reviewed all serious FAERS reports with fidaxomicin in the pediatric population (ages 0 - < 18 years) received by FDA from May 27, 2011, through June 5, 2023, and identified one case for inclusion in our case series. The case reported the adverse event of hallucinations and while the case described a temporal association with fidaxomicin and a positive dechallenge, other possible causes of hallucinations could not be ruled out. There was insufficient evidence to support a signal of hallucinations with fidaxomicin at this time. In our review of serious adverse events with fidaxomicin in the pediatric population, we did not identify any new safety signals or an increased severity or frequency of labeled adverse events and there were no deaths.

5 CONCLUSION

DPV did not identify any pediatric safety concerns for fidaxomicin at this time.

6 RECOMMENDATION

DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of fidaxomicin through routine pharmacovigilance.

7 REFERENCES

[1] Dificid (Fidaxomicin) [package insert]. San Diego, CA: Optimer Pharmaceuticals, Inc. May 27, 2011. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201699s000lbl.pdf. Accessed June 29, 2023.
[2] Dificid (fidaxomicin)[package insert]. Whitehouse Station, NJ: Merck & Co., Inc. January 24, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213138s000lbl.pdf. Accessed June 29, 2023.
[3] Center for Drug Evaluation and Research. Application Number 213128Orig1s000Multi-Discipline Review Dificid (fidaxomicin). January 24, 2020. Reference ID:4550912.
[4] Dificid (fidaxomicin)[package insert]. Whitehouse Station, NJ: Merck & Co, Inc. Revised May 28, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/201699s013,213138s001lbl.pdf. Accessed June 26, 2023.

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 Harmonization. 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.

8.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=1)

	Initial FDA Received Date	FAERS Case #	Version #	Central Triage Unit #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	6/10/2022	20951191	1	FDA-CDER-CTU-2022-46292	Direct	3	Female	USA	OT
	7/27/2022	*21141808*	*1*	*FDA-CDER-CTU-2022-59518*					

*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, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter and are coded as non-serious. A case may have more than one serious outcome.
Abbreviations: USA = United States of America, OT=other medically significant
Duplicates in italics.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KATE L MCCARTAN
08/29/2023 10:53:24 AM

IVONE E KIM
08/29/2023 10:57:40 AM

RACHNA KAPOOR
08/29/2023 11:16:55 AM

IDA-LINA DIAK
08/29/2023 11:43:27 AM