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:	October 24, 2023
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Product Name:	Sivextro (tedizolid phosphate)
Pediatric Labeling Approval Date:	June 19, 2020
Application Type/Numbers:	NDA 205436, NDA 205435
Applicant:	Cubist Pharmaceuticals, LLC
TTT Record ID:	2023-5745

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EXECUTIVE SUMMARY

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

The FDA approved tedizolid on June 20, 2014, for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adult patients. This review was prompted by pediatric labeling approved on June 19, 2020, to include pediatric patients 12 years of age and older.

DPV reviewed all serious FAERS reports with tedizolid in the pediatric population (ages 0 through 17 years), received by FDA through July 30, 2023. After a hands-on review, all reports were excluded from further discussion. There were no safety signals, no increased severity or frequency of labeled adverse events, and no pediatric deaths associated with tedizolid.

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

1 INTRODUCTION

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

1.1 PEDIATRIC REGULATORY HISTORY

Tedizolid, an oxazolidinone antibacterial agent that binds to the 50S subunit of the bacterial ribosome resulting in inhibition of protein synthesis, was first approved on June 20, 2014, for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant [MRSA] and methicillin-susceptible [MSSA] isolates), *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus anginosus* Group (including *Streptococcus anginosus, Streptococcus intermedius,* and *Streptococcus constellatus*), and *Enterococcus faecalis*.[1]

On June 19, 2020, the indication was expanded to include pediatric patients 12 years of age and older based on a randomized (3:1), single-blind, multicenter study comparing the safety and efficacy of tedizolid for the treatment of ABSSSI in patients 12 to less than 18 years of age. The study showed a high rate of clinical success at the test of cure visit which was similar in the tedizolid and comparator arms. Findings in other efficacy endpoints were supportive of primary analysis findings. Adverse reactions in adolescent patients included phlebitis (3%), increased hepatic transaminases (3%), and vomiting (1%). There were no deaths, and no serious adverse events related to tedizolid administration. The safety profile of tedizolid in adolescents were comparable to that in adults.[2]

This pediatric postmarketing pharmacovigilance review was prompted by the pediatric labeling changes on June 19, 2020. DPV has not previously presented tedizolid to the Pediatric Advisory Committee.

Tedizolid is available as a 200 mg, sterile lyophilized powder, in a single-dose vial for reconstitution and as a 200 mg tablet. The recommended dosage of tedizolid in pediatric patients is 200 mg once daily for 6 days either orally or as an intravenous (IV) infusion over 1 hour.[1]

1.2 RELEVANT LABELED SAFETY INFORMATION

The tedizolid labeling includes the following safety information (excerpted from the pertinent sections). For further tedizolid labeling information, including dosage and administration for adult patients, please refer to the full prescribing information.[1]

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

- Patients with neutropenia: The safety and efficacy of SIVEXTRO in patients with neutropenia (neutrophil count < 1000 cells/mm^3) have not been adequately evaluated. In an animal model of infection, the antibacterial activity of SIVEXTRO was reduced in the absence of granulocytes. Consider alternative therapies in neutropenic patients. (5.1)
- *Clostridioides difficile*-associated diarrhea: Evaluate if diarrhea occurs. (5.2)

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

The most common adverse reactions (≥ 2%) in adults are nausea, headache, diarrhea, infusion- or injection-related adverse reactions, vomiting, and dizziness. The most common adverse reactions (≥ 2%) in pediatric patients are phlebitis and increased hepatic transaminases. (6)

----------DRUG INTERACTIONS----------

SIVEXTRO (when administered orally) can increase the plasma concentrations of orally administered Breast Cancer Resistance Protein (BRCP) substrates. Monitor for adverse reactions related to the concomitant BRCP substrates if coadministration cannot be avoided. (7, 12.3)

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

Pregnancy: Based on animal data, SIVEXTRO may cause fetal harm. Advise pregnant women of the potential risks to a fetus. (8.1)

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	July 31, 2023
Time period of search	All reports through – July 30, 2023
Search type	RxLogix PV Reports Quick Query
Product terms	PAI: tedizolid, tedizolid phosphate
MedDRA search terms (Version 26.0)	All PT terms
* See Appendix A for a description of the FAERS database. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term, PAI = Product Active Ingredient	

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 through July 30, 2023 with tedizolid.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA Through July 30, 2023 With Tedizolid

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 18 years)	343 (152)	240 (53)	27 (4)
Pediatrics (0 - <18 years)	9 (8)	7 (6)	0 (0)

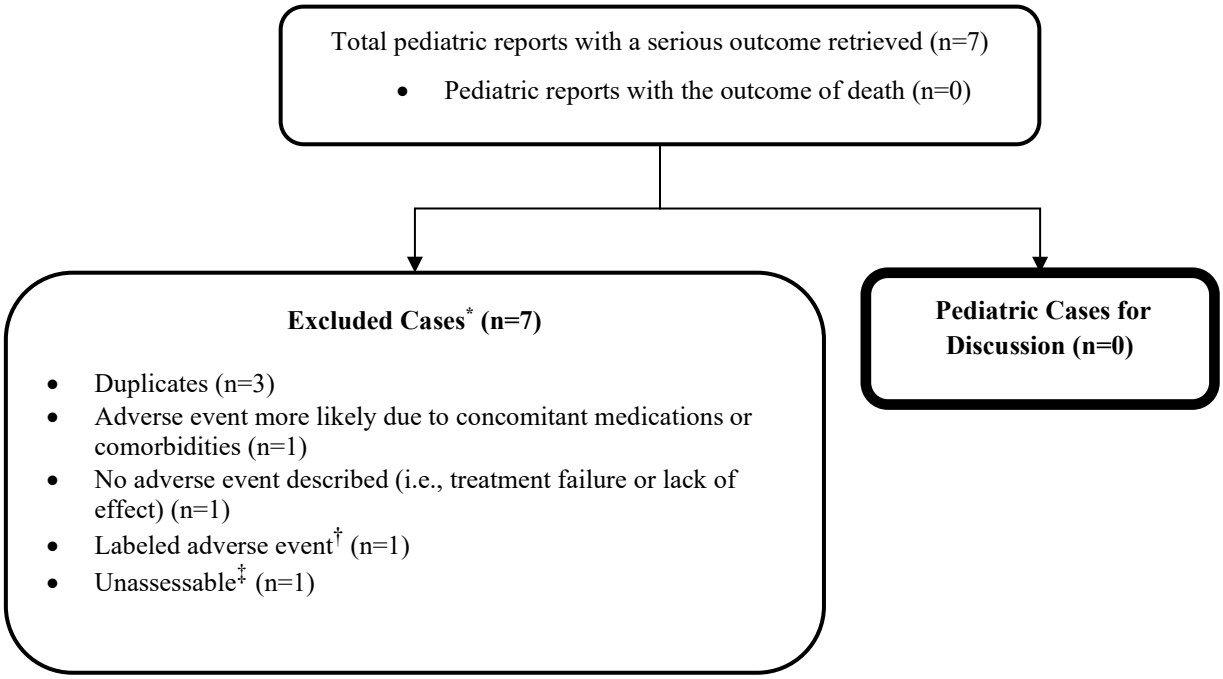
* May include duplicates and transplacental exposures, and have not been assessed for causality
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.

3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved seven serious pediatric reports through July 30, 2023.

We reviewed all FAERS pediatric reports with a serious outcome. We excluded reports from the case series for the following reasons: if the adverse event was more likely due to comorbidities and/or concomitant medication (n=1), no adverse event described (n=1), duplicate report (n=3), unassessable (n=1), or a labeled adverse event (n=1). **Figure 1** presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious Pediatric Cases with Tedizolid



* DPV reviewed these cases, but they were excluded from further discussion for the reasons listed above.
† Labeled adverse event does not represent increased severity or frequency.

‡ Unassessable: Case cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, clinical course) or the information is contradictory or information 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 Case (N=0)

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

4 DISCUSSION

DPV reviewed all serious FAERS reports with tedizolid use in the pediatric population (ages 0 through 17 years), received by FDA for all dates through July 30, 2023. The FAERS search identified seven serious pediatric reports. After hands-on review, all reports were excluded from further discussion. There were no safety signals, no increased severity or frequency of labeled adverse events, and no pediatric deaths associated with tedizolid.

5 CONCLUSION

DPV did not identify any pediatric safety concerns for tedizolid 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 tedizolid through routine pharmacovigilance.

7 REFERENCES

[1] Sivextro (tedizolid phosphate) [package insert]. Whitehouse Station, NJ. Merck & Co., Inc. Revised November 2021. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/205435s014,205435s009lbl.pdf. Accessed on August 7, 2023.
[2] Gopalaswamy R. Sivextro (tedizolid phosphate) Multi-Disciplinary Review and Evaluation. June 16, 2020. Available at: https://www.fda.gov/media/140675/download?attachment. Accessed on August 7, 2023.

8 APPENDICES

8.1 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 (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.

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