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 15, 2025
Reviewers:	Lindsey Buscemi, PharmD, BCPS, AAHIVP, Safety Evaluator Division of Pharmacovigilance II Ivone Kim, MD, Medical Officer Division of Pharmacovigilance I
Team Leader:	Rachna Kapoor, PharmD, MBA Division of Pharmacovigilance II
Division Director:	S. Christopher Jones PharmD, MPH, MS Division of Pharmacovigilance II
Product Name:	Zinplava (bezlotoxumab)
Pediatric Labeling Approval Date:	May 26, 2023
Application Type/Number:	BLA 761046
Applicant:	Merck & Co., Inc.
TTT Record ID:	2025-15331

TABLE OF CONTENTS

Executive Summary 1
1 Introduction 2
1.1 Pediatric Regulatory History 2
1.2 Relevant Labeled Safety Information 2
2 Methods and Materials 3
3 Results 3
3.1 Selection of U.S. Serious Pediatric Cases in FAERS 3
3.2 Summary of U.S. Fatal Pediatric Cases (N=0) 3
3.3 Summary of U.S. Serious Non-Fatal Pediatric Cases (N=0) 3
4 Discussion 3
5 Conclusion 3
6 References 4
7 Appendices 4
7.1 Appendix A. FDA Adverse Event Reporting System (FAERS) 4

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Zinplava (bezlotoxumab) 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 bezlotoxumab in pediatric patients.

Zinplava (bezolutoxumab) is a humanized monoclonal antibody that binds to *Clostridioides difficle* toxin B, initially FDA approved on October 21, 2016. Bezlotoxumab is currently indicated to reduce recurrence of *Clostridioides difficile* infection (CDI) in adults and pediatric patients 1 year of age and older who are receiving antibacterial treatment for CDI and are at a high risk for CDI recurrence.

This pediatric postmarketing safety review was prompted by pediatric labeling on May 26, 2023, which expanded the indication for use to include pediatric patients 1 year to less than 18 years of age.

A pediatric postmarket pharmacovigilance review for bezlotoxumab has not previously been presented to the Pediatric Advisory Committee.

DPV searched FAERS for all U.S. serious reports with bezlotoxumab in pediatric patients less than 18 years of age from October 21, 2016, through July 1, 2025, and did not identify any reports.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with bezlotoxumab in pediatric patients less than 18 years of age.

DPV will continue routine pharmacovigilance monitoring for bezlotoxumab.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Zinplava (bezlotoxumab) 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 bezlotoxumab in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Zinplava (bezlotoxumab) is a human monoclonal antibody that binds to *Clostridioides difficile* toxin B and neutralizes its effects.[1] Bezlotoxumab was initially FDA approved on October 21, 2016. Bezlotoxumab is currently indicated to reduce recurrence of *Clostridioides difficile* infection (CDI) in adults and pediatric patients 1 year of age and older who are receiving antibacterial treatment for CDI and are at a high risk for CDI recurrence.[1]

This pediatric postmarketing safety review was prompted by pediatric labeling on May 26, 2023, which expanded the use of bezlotoxumab to reduce recurrence of CDI in patients who are receiving antibacterial drug treatment for CDI and are at a high risk for CDI recurrence to include patients 1 year to less than 18 years of age.[2]

A pediatric postmarket pharmacovigilance review for bezlotoxumab has not previously been presented to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The bezlotoxumab labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional bezlotoxumab labeling information, please refer to the full prescribing information.[1]

---------- CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS ----------
Heart Failure: Was reported more commonly in ZINPLAVA-treated patients with a history of congestive heart failure (CHF) in Trial 1 and Trial 2. In patients with a history of CHF, ZINPLAVA should be reserved for use when the benefit outweighs the risk. (5.1)

----------ADVERSE REACTIONS ----------
- Adult Patients: The most common adverse reactions (reported in =4% of adult patients) included nausea, pyrexia, and headache. (6.1)
- Pediatric Patients: The most common adverse reactions (reported in >10% of pediatric patients) were pyrexia and headache (6.1)

8.4 Pediatric Use
The safety and effectiveness of ZINPLAVA to reduce recurrence of CDI have been established in pediatric patients 1 year of age and older. Use of ZINPLAVA in pediatric patients 1 year of age and older is supported by evidence from adequate and well-controlled trials in adults with additional pharmacokinetic and safety data in pediatric patients aged 1 year and older. The adverse reactions and the pharmacokinetics observed in pediatric patients were comparable to that observed in adult patients [see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)].

2 METHODS AND MATERIALS

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

Table 1. FAERS Search Strategy[*]

Date of search	July 2, 2025
Time period of search	October 21, 2016[†] - July 1, 2025
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product active ingredient: bezlotoxumab
MedDRA search terms (Version 28.0)	All Preferred Terms
Other criteria	Case Seriousness: Serious[‡] Country Derived: USA

[*] See Appendix A for a description of the FAERS database.
[†] U.S. Approval date
[‡] 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.
Abbreviation: MedDRA=Medical Dictionary for Regulatory Activities, USA=United States of America

3 RESULTS

3.1 SELECTION OF U.S. SERIOUS PEDIATRIC CASES IN FAERS

Our FAERS search did not retrieve any U.S. serious pediatric reports for patients less than 18 years old from October 21, 2016, through July 1, 2025.

3.2 SUMMARY OF U.S. FATAL PEDIATRIC CASES (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.3 SUMMARY OF U.S. SERIOUS NON-FATAL PEDIATRIC CASES (N=0)

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

4 DISCUSSION

DPV searched FAERS for all U.S. serious reports with bezlotoxumab in pediatric patients less than 18 years of age from October 21, 2016, through July 1, 2025, and did not identify any reports.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with bezlotoxumab in pediatric patients less than 18 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Zinplava (bezlotoxumab) [package insert]. Rahway, NJ: Merck & Co., Inc. May 2023.
2. U.S. Food and Drug Administration. Supplemental BLA Approval Letter (S-012) for BLA 761046, Zinplava (bezlotoxumab). May 26, 2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/761046Orig1s012ltr.pdf.

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.