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 9, 2023
Medical Officer:	Ivone Kim, MD Division of Pharmacovigilance I (DPV-I)
Team Leader:	Carmen Cheng, PharmD Division of Pharmacovigilance I (DPV-I)
Director:	Monica Muñoz, PharmD, PhD Division of Pharmacovigilance I (DPV-I)
Product Name:	Otiprio (ciprofloxacin otic suspension)
Pediatric Labeling Approval Date:	March 2, 2018
Application Type/Number:	NDA 207986
Applicant:	ALK Abello
TTT Record ID:	2023-5050

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Otiprio (ciprofloxacin otic suspension) in pediatric patients through age 17 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Otiprio in pediatric patients.

FDA first approved Otiprio on December 10, 2015, for the treatment of pediatric patients (6 months of age and older) with bilateral otitis media with effusion undergoing tympanostomy tube placement. On March 2, 2018, the Otiprio indication was expanded to include treatment of acute otitis externa in patients 6 months of age and older due to *Pseudomonas aeruginosa* and *Staphylococcus aureus*. This review was stimulated by the pediatric labeling change for Otiprio on March 2, 2018.

DPV searched FAERS for all reports with Otiprio in pediatric patients received by FDA from October 28, 2017, through May 31, 2023, and retrieved one pediatric report with a serious outcome. DPV reviewed the report and excluded it from further discussion as it did not describe exposure to Otiprio.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths associated with Otiprio in pediatric patients aged 0 through 17 years old. DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of Otiprio.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Otiprio (ciprofloxacin otic suspension) in pediatric patients through age 17 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on U.S. serious unlabeled adverse events associated with Otiprio in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

FDA first approved Otiprio on December 10, 2015, for the treatment of pediatric patients (6 months of age and older) with bilateral otitis media with effusion undergoing tympanostomy tube placement.[1] On March 2, 2018, the Otiprio indication was expanded to include treatment of acute otitis externa in patients 6 months of age and older due to *Pseudomonas aeruginosa* and *Staphylococcus aureus*. This review was stimulated by the pediatric labeling change for Otiprio on March 2, 2018.

DPV previously performed a pediatric postmarketing pharmacovigilance review for Otiprio for the Pediatric Advisory Committee. The DPV review, dated November 16, 2017, did not identify new safety concerns with Otiprio and DPV recommended routine monitoring for adverse events with Otiprio.[3]

1.2 RELEVANT LABELED SAFETY INFORMATION[2]

The Otiprio labeling provides the following relevant safety information excerpted from the Highlights of Prescribing Information and *Pediatric Use* sections. For additional Otiprio labeling information, please refer to the full prescribing information.

CONTRAINDICATIONS

OTIPRIO is contraindicated in patients with a history of hypersensitivity to ciprofloxacin, to quinolones, or to any component of OTIPRIO. (4)

WARNINGS AND PRECAUTIONS

Potential for Microbial Overgrowth: OTIPRIO may result in overgrowth of non-susceptible bacteria and fungi. (5.1)

ADVERSE REACTIONS

Otitis Media with Effusion: The most frequently occurring adverse reactions (with an incidence rate greater than 3%) were nasopharyngitis and irritability. (6.1)

Acute Otitis Externa: The most frequently occurring adverse reactions (with an incidence rate of at least 2%) were: ear pruritus, headache, otitis media and ear discomfort. (6.1)

8.4 Pediatric Use

The safety and effectiveness of OTIPRIO for the treatment of pediatric patients (6 months of age and older) with bilateral otitis media with effusion undergoing tympanostomy tube placement was established in 530 patients who participated in the Phase 3 trials. The median age of patients enrolled in the clinical trials was 1.5 years; 62% of patients were 6 months through 2 years of age and 38% of patients were greater than 2 years of age [see Adverse Reactions (6.1) and Clinical

Studies (14)]. The safety and effectiveness of OTIPRIO for the treatment of acute otitis externa was established in 67 pediatric patients (3 through 17 years of age) who participated in the Phase 3 trial; 57% of patients were 3 through 11 years of age and 43% of patients were 12 through 17 years of age. The safety and efficacy observed in the pediatric patients was no different from the older population. OTIPRIO is indicated for the treatment of acute otitis externa in pediatric patients 6 months of age and older [see Indications and Usage (1), Dosage and Administration (2), Adverse Reactions (6.1) and Clinical Studies (14)]. The safety and effectiveness of OTIPRIO in infants below 6 months of age have not been established for the treatment of pediatric patients with bilateral otitis media with effusion undergoing tympanostomy tube placement and acute otitis externa.

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 7, 2023
Time period of search	October 28, 2017† through May 31, 2023
Search type	Drug Safety Analytics Dashboard Quick Query
Product terms	Product name: Otiprio Application: NDA 207986
MedDRA search terms (Version 26.0)	All Preferred Terms
* See Appendix A for a description of the FAERS database. † Data-lock date from previous DPV pediatric postmarketing review for Otiprio Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities	

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 received by FDA through May 30, 2023, with Otiprio.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From October 28, 2017, Through May 31, 2023, with Otiprio			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	4 (1)	1 (1)	0 (0)
Pediatrics (0 - <18 years)	1 (1)	1 (1)	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

The FAERS search retrieved one pediatric report with a serious outcome. DPV reviewed the report and excluded it from further discussion as it did not describe exposure to Otiprio.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

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

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

We did not identify cases in FAERS with Otiprio in the pediatric population reporting a non-fatal serious outcome.

4 DISCUSSION

DPV searched FAERS for all reports with Otiprio in pediatric patients received by FDA from October 28, 2017, through May 31, 2023, but did not identify any cases for discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths associated with Otiprio in pediatric patients aged 0 through 17 years old.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for Otiprio 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 Otiprio.

7 REFERENCES

1. Nambiar S. Otiprio NDA 207986 Summary Review. December 10, 2015. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207986Orig1s000SumR.pdf

2. Otiprio (ciprofloxacin otic suspension) for intratympanic for otic use [package insert]. San Diego, CA: Otonomy, Inc.; March 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/207986s002lbl.pdf

3. Wassel R. Pediatric Postmarketing Pharmacovigilance Review. November 16, 2017. Available at: https://www.fda.gov/media/110536/download

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.

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/

IVONE E KIM
08/09/2023 02:23:59 PM

DEBRA L RYAN on behalf of CARMEN CHENG
08/10/2023 04:40:49 PM

MONICA MUNOZ
08/10/2023 05:02:31 PM