Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	November 16, 2017
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Product Name:	OTIPRIO (6% ciprofloxacin otic suspension)
Pediatric Labeling Approval Date:	December 10, 2015
Application Type/Number:	NDA 207986
Applicant/Sponsor:	Otonomy, Inc.
OSE RCM #:	2017-2215

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome for OTIPRIO (6% ciprofloxacin otic suspension) in pediatric patients.

OTIPRIO (6% ciprofloxacin otic suspension) was approved on December 10, 2015, and is indicated for the treatment of pediatric patients with bilateral otitis media with effusion undergoing tympanostomy tube placement.

There was one serious adverse event case in a patient of unknown age, assumed to be a pediatric patient, during this time period, although it was likely related to the patient's underlying condition.

There is no evidence from these data that there are new pediatric safety concerns with this drug at this time.

We will continue to monitor adverse events associated with the use of OTIPRIO.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

OTIPRIO (6% ciprofloxacin otic suspension) is available as an otic suspension for intratympanic administration indicated for the treatment of pediatric patients with bilateral otitis media with effusion undergoing tympanostomy tube (TT) placement.

Compared to other otic ciprofloxacin preparations, the dosage form, treatment indication, regimen, and route of administration of OTIPRIO are new. OTIPRIO is formulated for a new route of administration, specifically intratympanic administration. Intratympanic administration is a method of otic administration performed during myringotomy and TT placement surgery. This route of administration is intended to follow suctioning of middle ear effusion and refers to injecting the drug through the myringotomy site (intratympanic injection) prior to the actual placement of the TT.

At the time of approval, OTIPRIO's label stated that safety and effectiveness were established in 530 pediatric patients with bilateral otitis media with middle ear effusion undergoing myringotomy with tympanostomy tube placement. The median age of patients enrolled in the clinical trials was 1.5 years. The safety and effectiveness in infants below 6 months of age have not been established.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

PEDIATRIC USE

The safety and effectiveness of OTIPRIO in infants below six months of age have not been established.

The safety and effectiveness of OTIPRIO were established in 530 pediatric patients with bilateral otitis media with middle ear effusion undergoing myringotomy with tympanostomy tube placement. 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.

2 POSTMARKET ADVERSE EVENT REPORTS

2.1 METHODS AND MATERIALS

2.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in Table 2.1.1. See Appendix A for a description of the FAERS database.

Table 2.1.1 FAERS Search Strategy

Date of Search	October 27, 2017
Time Period of Search	December 10, 2015* - October 27, 2017†
Search Type	Mercado Quick Search Drug Safety Analytics
Product Names	Product Name – Otiprio Verbatim Product – Otiprio
Search Parameters	All ages, all outcomes, worldwide

** FDA approval date*

† There may be reports received in this time period that were not captured because they had not been entered into FAERS by the time of the search.

2.2 RESULTS

2.2.1 Total Number of FAERS Reports by Age

Table 2.2.1 Total Adult and Pediatric FAERS reports* received by FDA since December 10, 2015, and entered into FAERS before October 27, 2017, with OTIPRIO (6% ciprofloxacin otic suspension)

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	0 (0)	0 (0)	0 (0)
Pediatrics (0 - <17 years)	1 (1)	0 (0)	0 (0)
Not reported	20 (20)	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, and other serious important medical events.

We include serious reports in which the patient's age was not reported because the drug is only indicated in pediatric patients.

2.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=0)

There were no fatal pediatric adverse event cases.

2.4 SUMMARY OF NON-FATAL SERIOUS ADVERSE EVENT CASES (N=1)

The one case (no demographic information provided) reported as serious described the event as "the day after OTIPRIO administration, the patient experienced hearing loss. As of [the date reported to the manufacturer], the status of product use and the event were unknown. No additional information was provided."

Reviewer comment: The case report had insufficient clinical information to assess; however, decreased hearing (permanent or temporary) is reported with various forms of otitis including acute otitis media with effusion and chronic otitis.[1-3]

3 DISCUSSION

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events and there were no deaths associated with OTIPRIO.

4 CONCLUSION

There is no evidence from these data that there are new pediatric safety concerns with this drug at this time.

5 RECOMMENDATIONS

We will continue to monitor adverse events associated with the use of OTIPRIO.

6 REFERENCES

1. Whittemore KR Jr, Dornan BK, Lally T, Dargie JM. Persistent conductive or mixed hearing loss after the placement of tympanostomy tubes. Int J Pediatr Otorhinolaryngol. 2012 Oct;76(10):1465-70.

2. Homøe P, Kværner K, Casey JR, Damoiseaux RA, van Dongen TM, Gunasekera H, Jensen RG, Kvestad E, Morris PS, Weinreich HM. Panel 1: Epidemiology and Diagnosis. Otolaryngol Head Neck Surg. 2017 Apr;156(4_suppl):S1-S21.

3. Schilder AG, Marom T, Bhutta MF, Casselbrant ML, Coates H, Gisselsson-Solén M, Hall AJ, Marchisio P, Ruohola A, Venekamp RP, Mandel EM. Panel 7: Otitis Media: Treatment and Complications. Otolaryngol Head Neck Surg. 2017 Apr;156(4_suppl):S88-S105.

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 the FDA's postmarketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference 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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/s/

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