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:	April 24, 2018
Safety Evaluator:	Ronald Wassel, PharmD Division of Pharmacovigilance II (DPV II)
Team Leader:	Kelly Cao, PharmD DPV II
Deputy Division Director:	Ida-Lina Diak, PharmD, MS DPV II
Product Name:	OTOVEL (ciprofloxacin and fluocinolone acetonide) otic solution
Pediatric Labeling Approval Date:	April 29, 2016
Application Type/Number:	NDA 208251
Applicant/Sponsor:	Laboratorios SALVAT, S.A.
OSE RCM #:	2018-488

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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 for OTOVEL (ciprofloxacin and fluocinolone acetonide) otic solution in pediatric patients.

OTOVEL was first approved in 2016 and is indicated for the treatment of acute otitis media with tympanostomy tubes (AOMT) in pediatric patients (aged 6 months and older) due to *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa*.

There were no pediatric serious adverse event cases identified in the FDA Adverse Event Reporting System (FAERS) database during this time period; however, we identified three non-serious adverse event cases reported in pediatric patients.

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

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

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

OTOVEL (ciprofloxacin and fluocinolone acetonide) is available as an otic solution indicated for the treatment of AOMT in pediatric patients (aged 6 months and older) due to *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa*.

Based on clinical efficacy and safety data submitted by the Applicant from two randomized, double-blind, active-controlled clinical trials prior to approval, there was adequate evidence of safety and efficacy for OTOVEL Otic Solution in the twice daily dosing regimen for the treatment of AOMT in pediatric patients (aged 6 months and older). OTOVEL was found to be safe and well tolerated. Adverse events reported more frequently in the OTOVEL group were pyrexia, otitis media, rhinorrhea, cough, upper respiratory tract infection and otorrhea.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

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

OTOVEL is contraindicated in:

- Patients with known hypersensitivity to fluocinolone acetonide or other corticosteroids, ciprofloxacin or other quinolones, or to any component of OTOVEL.
- Viral infections of the external ear canal, including varicella and herpes simplex infections and fungal otic infections.

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

- *Hypersensitivity*: Discontinue use at the first appearance of a skin rash or any other sign of hypersensitivity.
- *Potential for Microbial Overgrowth:* Prolonged use may result in the overgrowth of non-susceptible bacteria and fungi. If such infections occur, discontinue use and institute alternative therapy.

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

The most common adverse reactions that occurred in ≥1 patient were otorrhea, excessive granulation tissue, ear infection, ear pruritus, tympanic membrane disorder, auricular swelling and balance disorder.

----------PEDIATRIC USE----------

OTOVEL has been studied in patients as young as 6 months in adequate and well-controlled clinical trials. No major differences in safety and effectiveness have been observed between adult and pediatric patients.

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	March 6, 2018
Time Period of Search	April 29, 2016* - March 5, 2018
Search Type	Mercado Quick Search Drug Safety Analytics
Product Names	Product Name – Otovel Product Active Ingredient – Ciprofloxacin\Fluocinolone Acetonide
Search Parameters	All ages, all outcomes, worldwide

* *U.S. Approval date*

2.2 RESULTS

2.2.1 Total Number of FAERS Reports by Age

Table 2.2.1 Total Adult and Pediatric FAERS reports* from April 29, 2016, through March 5, 2018, with OTOVEL (ciprofloxacin and fluocinolone acetonide) otic Solution

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	16 (4)	14 (2)	0 (0)
Pediatrics (0 - <17 years)	3‡ (3)	0 (0)	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.

‡ Three reports of pediatric patients were identified among reports not reporting an age.

2.2.2 Selection of Pediatric Cases in FAERS

We identified three pediatric cases associated with OTOVEL use, none of which reported a serious outcome. All three were coded as null age reports but identified as pediatric cases based on information in the narratives. Because OTOVEL is specifically indicated for AOMT in pediatric patients, we reviewed all the null age reports to see if the narrative mentioned whether the individual was a pediatric patient.

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 PEDIATRIC ADVERSE EVENT CASES (N=3)

The reported events included development of granulation tissue, application site "stinging/burning," and "fluid discharge" from the ear canal (otorrhea), which are all labeled events.

3 DISCUSSION

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events and there were no deaths reported in the pediatric population with OTOVEL.

4 CONCLUSION

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

5 RECOMMENDATIONS

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

6 APPENDICES

6.1 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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RONALD T WASSEL
04/24/2018

KELLY Y CAO
04/25/2018

IDA-LINA DIAK
04/25/2018