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 29, 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:	Zerviate (cetirizine ophthalmic solution)
Pediatric Labeling Approval Date:	May 30, 2017
Application Type/Number:	NDA 208694
Applicant:	Eyevance Pharmaceuticals, LLC
TTT Record ID:	2023-5072

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Zerviate (cetirizine ophthalmic solution) in pediatric patients through age 16 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Zerviate in pediatric patients.

The FDA approved Zerviate on May 30, 2017, and it is indicated for treatment of ocular itching associated with allergic conjunctivitis. The safety and effectiveness of Zerviate was established in pediatric patients 2 years of age and older. Use of Zerviate in these pediatric patients is supported by evidence from adequate and well-controlled studies in pediatric and adult patients. This review was stimulated by the pediatric labeling at Zerviate approval.

DPV searched the FAERS data for all reports with Zerviate in pediatric patients received by FDA through May 31, 2023, and did not identify any reports. Therefore, there were no new safety signals identified, no increased severity of labeled adverse events, and no deaths associated with Zerviate in pediatric patients aged 0 through 16 years.

DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of Zerviate.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Zerviate (cetirizine ophthalmic solution) in pediatric patients through age 16 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Zerviate in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

The FDA approved Zerviate on May 30, 2017, and it is indicated for treatment of ocular itching associated with allergic conjunctivitis. The safety and effectiveness of Zerviate was established in pediatric patients 2 years of age and older. Use of Zerviate in these pediatric patients is supported by evidence from three randomized double-masked, placebo-controlled, conjunctival allergen challenge clinical trials in pediatric and adult patients with a history of allergic conjunctivitis.[1]

This review was stimulated by the pediatric labeling at Zerviate approval. Zerviate has not been previously presented to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION[1]

The Zerviate labeling provides the following relevant safety information excerpted from the WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, and *Pediatric Use* sections. For additional Zerviate labeling information, please refer to the full prescribing information.

> **5 WARNINGS AND PRECAUTIONS**
> **5.1 Contamination of Tip and Solution**
> As with any eye drop, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle or tip of the single-use container in order to avoid injury to the eye and to prevent contaminating the tip and solution. Keep the multi-dose bottle closed when not in use. Discard the single-use container after using in each eye.
>
> **5.2 Contact Lens Wear**
> Patients should be advised not to wear a contact lens if their eye is red. ZERVIATE should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of ZERVIATE. The preservative in ZERVIATE, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted 10 minutes following administration of ZERVIATE.
>
> **6 ADVERSE REACTIONS**
> Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trial of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates in practice. In seven clinical trials, patients with allergic conjunctivitis or those at a risk of developing allergic conjunctivitis received one drop of either cetirizine (N=511) or vehicle (N=329) in one or both eyes. The most commonly reported adverse

reactions occurred in approximately 1–7% of patients treated with either ZERVIATE or vehicle. These reactions were ocular hyperemia, instillation site pain, and visual acuity reduced.

8.4 Pediatric Use

The safety and effectiveness of ZERVIATE™ (cetirizine ophthalmic solution) 0.24% has been established in pediatric patients two years of age and older. Use of ZERVIATE in these pediatric patients is supported by evidence from adequate and well-controlled studies of ZERVIATE in pediatric and adult patients.

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	All dates through May 31, 2023
Search type	Drug Safety Analytics Dashboard Quick Query
Product terms	Product name: Zerviate Application: NDA 208694
MedDRA search terms (Version 26.0)	All Preferred Terms
* See Appendix A for a description of the FAERS database. 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 31, 2023, with Zerviate.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA Through May 31, 2023, with Zerviate			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	1 (1)	0 (0)	0 (0)
Pediatrics (0 - <17 years)	0 (0)	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, or other serious important medical events.			

3.1.2 Summary of Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

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

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

4 DISCUSSION

DPV searched FAERS for all reports with Zerviate in pediatric patients received by FDA through May 31, 2023, but did not identify any reports.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths associated with Zerviate in pediatric patients aged 0 through 16 years old.

5 CONCLUSION

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

7 REFERENCES

1. Zerviate (cetirizine ophthalmic solution) 0.24% for ophthalmic use [package insert]. Fort Worth, TX: Eyevance Pharmaceuticals, LLC.; February 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208694s006lbl.pdf

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 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
08/29/2023 10:57:01 AM

CARMEN CHENG
08/29/2023 10:58:31 AM

MONICA MUNOZ
08/29/2023 11:00:23 AM