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:	November 8, 2023
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Product Name:	Ciloxan (ciprofloxacin ophthalmic solution)
Pediatric Labeling Approval Date:	March 21, 2017
Application Type/Number:	NDA 019992
Applicant:	Novartis
TTT Record ID:	2023-6134

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Ciloxan (ciprofloxacin ophthalmic solution) in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA). This review focuses on serious unlabeled adverse events associated with Ciloxan in pediatric patients.

Ciloxan (ciprofloxacin ophthalmic solution) is a fluoroquinolone antibacterial active against a broad spectrum of gram-positive and gram-negative ocular pathogens. It was initially approved in the U.S. on December 31, 1990. Ciloxan ophthalmic solution is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

Corneal Ulcers:	*Pseudomonas aeruginosa* *Serratia marcescens* *Staphylococcus aureus* *Staphylococcus epidermidis* *Streptococcus pneumoniae* *Streptococcus* (Viridans Group)	Conjunctivitis:	*Haemophilus influenzae* *Staphylococcus aureus* *Staphylococcus epidermidis* *Streptococcus pneumoniae*

Ciprofloxacin is available in another ophthalmic formulation as Ciloxan ophthalmic ointment (NDA 020369). Ciloxan ophthalmic ointment was initially approved in the U.S. on March 30, 1998, and it is currently indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of gram-positive microorganisms (*Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Streptococcus* (Viridans Group)) and gram-negative microorganisms (*Haemophilus influenzae).*

This pediatric postmarketing safety review was prompted by pediatric labeling on March 21, 2017, that expanded the indication to include use in pediatric patients younger than 1 year old. A pediatric safety review for Ciloxan has not previously been presented to the Pediatric Advisory Committee.

DPV reviewed all serious FAERS reports with Ciloxan in pediatric patients less than 17 years of age from December 31, 1990 – August 29, 2023. DPV identified 31 reports, however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with Ciloxan in pediatric patients less than 17 years of age.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Ciloxan (ciprofloxacin ophthalmic solution) in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA). This review focuses on serious unlabeled adverse events associated with Ciloxan in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Ciloxan (ciprofloxacin ophthalmic solution) is a fluoroquinolone antibacterial active against a broad spectrum of gram-positive and gram-negative ocular pathogens. It was initially approved in the U.S. on December 31, 1990. Ciloxan ophthalmic solution is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below:[1]

Corneal Ulcers:	*Pseudomonas aeruginosa* *Serratia marcescens* *Staphylococcus aureus* *Staphylococcus epidermidis* *Streptococcus pneumoniae* *Streptococcus* (Viridans Group)	Conjunctivitis:	*Haemophilus influenzae* *Staphylococcus aureus* *Staphylococcus epidermidis* *Streptococcus pneumoniae*

Ciprofloxacin is available in another ophthalmic formulation as Ciloxan ophthalmic ointment (NDA 020369). Ciloxan ophthalmic ointment was initially approved in the U.S. on March 30, 1998, and it is currently indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of gram-positive microorganisms (*Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Streptococcus* (Viridans Group)) and gram-negative microorganisms (*Haemophilus influenzae).* The safety and effectiveness of Ciloxan ophthalmic ointment in pediatric patients below the age of two years have not been established.[2]

This pediatric postmarketing safety review was prompted by pediatric labeling for Ciloxan ophthalmic solution on March 21, 2017, that expanded the indication to include use in pediatric patients younger than 1 year old. A pediatric safety review for Ciloxan has not previously been presented to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The Ciloxan ophthalmic solution labeling contains the following safety information excerpted from the CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections of the product labeling. For additional Ciloxan ophthalmic solution labeling information, please refer to the full prescribing information.[1]

> **CONTRAINDICATIONS:**
> A history of hypersensitivity to ciprofloxacin or any other component of the medication is a contraindication to its use. A history of hypersensitivity to other quinolones may also contraindicate the use of ciprofloxacin.
>
> **WARNINGS:**
> NOT FOR INJECTION INTO THE EYE.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reactions. Serious anaphylactic reactions require immediate emergency treatment with epinephrine and other resuscitation measures, including oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated. Remove contact lenses before using.

PRECAUTIONS:

General: As with other antibacterial preparations, prolonged use of ciprofloxacin may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

Ciprofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity reaction.

In clinical studies of patients with bacterial corneal ulcer, a white crystalline precipitate located in the superficial portion of the corneal defect was observed in 35 (16.6%) of 210 patients. The onset of the precipitate was within 24 hours to 7 days after starting therapy. In one patient, the precipitate was immediately irrigated out upon its appearance. In 17 patients, resolution of the precipitate was seen in 1 to 8 days (seven within the first 24 to 72 hours), in five patients, resolution was noted in 10 to 13 days. In nine patients, exact resolution days were unavailable; however, at follow-up examinations, 18 to 44 days after onset of the event, complete resolution of the precipitate was noted. In three patients, outcome information was unavailable. The precipitate did not preclude continued use of ciprofloxacin, nor did it adversely affect the clinical course of the ulcer or visual outcome. (SEE ADVERSE REACTIONS).

Information for patients: Do not touch dropper tip to any surface, as this may contaminate the solution.

Drug Interactions: Specific drug interaction studies have not been conducted with ophthalmic ciprofloxacin. However, the systemic administration of some quinolones has been shown to elevate plasma concentrations of theophylline, interfere with the metabolism of caffeine, enhance the effects of the oral anticoagulant, warfarin, and its derivatives, and has been associated with transient elevations in serum creatinine in patients receiving cyclosporine concomitantly.

Pediatric Use: The safety and effectiveness of CILOXAN (ciprofloxacin ophthalmic solution) 0.3% have been established in all ages. Use of CILOXAN is supported by evidence from adequate and well controlled studies of CILOXAN in adults, children and neonates [see Clinical Studies]. Although ciprofloxacin and other quinolones cause arthropathy in immature animals after oral administration, topical ocular administration of ciprofloxacin to immature animals did not cause any arthropathy and there is no evidence that the ophthalmic dosage form has any effect on the weight bearing joints.

ADVERSE REACTIONS:

The most frequently reported drug related adverse reaction was local burning or discomfort. In corneal ulcer studies with frequent administration of the drug, white crystalline precipitates were seen in approximately 17% of patients (SEE PRECAUTIONS). Other reactions occurring in less than 10% of patients included lid margin crusting, crystals/scales, foreign body sensation, itching, conjunctival hyperemia and a bad taste following instillation. Additional events occurring in less than 1% of patients included corneal staining, keratopathy/keratitis, allergic reactions, lid edema, tearing, photophobia, corneal infiltrates, nausea and decreased vision.

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	August 30, 2023
Time period of search	December 31, 1990† - August 29, 2023
Search type	Drug Safety Analytics Dashboard (DSAD) Quick Query
Product terms	Product Name: Ciloxan NDA: 019992, 020369
MedDRA search terms (Version 26.0)	All Preferred Terms
* See Appendix A for a description of the FAERS database. † Ciloxan ophthalmic solution (NDA 019992) U.S. approval date. Abbreviations: NDA=New Drug Application, MedDRA=Medical Dictionary for Regulatory Activities	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

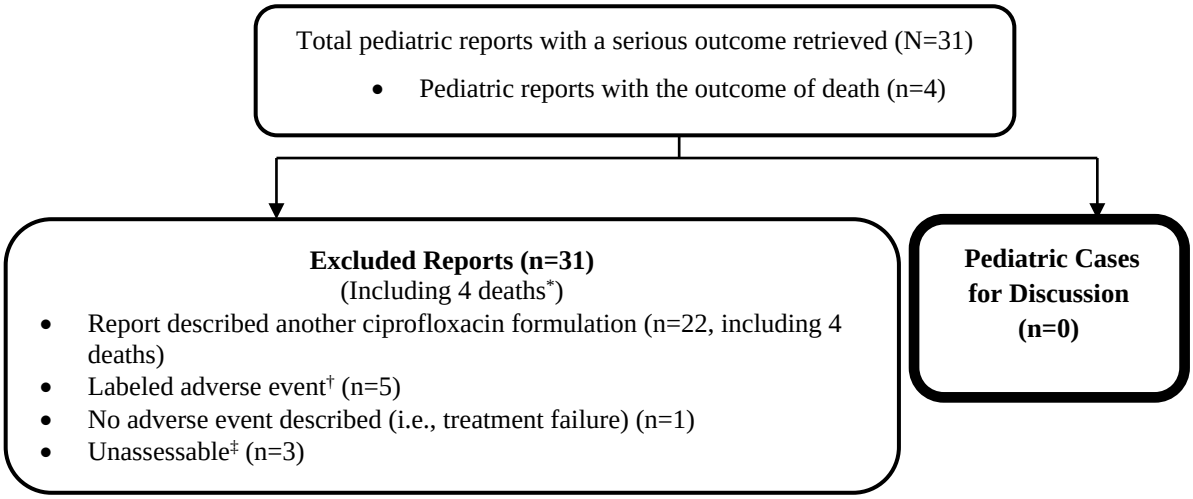
Table 2 presents the number of adult and pediatric FAERS reports from December 31, 1990 – August 29, 2023, with Ciloxan.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From December 31, 1990 – August 29, 2023, With Ciloxan			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	948 (130)	898 (81)	56 (3)
Pediatrics (0 - < 17 years)	35‡ (8)	31‡ (5)	4‡ (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. ‡ See Figure 1. One additional report of pediatric death was identified among reports not reporting an age. This report is reflected in the counts of pediatric reports.			

3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved 31 serious pediatric reports from December 31, 1990 – August 29, 2023. We reviewed all FAERS pediatric reports with a serious outcome. We excluded all 31 reports from the case series for the reasons listed in **Figure 1**. **Figure 1** presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious Pediatric Cases With Ciloxan



* Four excluded FAERS reports described fatal outcomes. All death reports involved other ciprofloxacin formulations. None of the deaths were determined to be attributed to Ciloxan. Deaths were attributable to underlying sepsis and its complications.
† Labeled adverse event does not represent increased severity or frequency.
‡ Unassessable: The report cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome), the information is contradictory, or information provided in the report cannot be supplemented or verified.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

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

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

4 DISCUSSION

DPV reviewed all serious FAERS reports with Ciloxan in pediatric patients less than 17 years of age from December 31, 1990 – August 29, 2023. DPV identified 31 reports; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with Ciloxan in pediatric patients less than 17 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Ciloxan (ciprofloxacin) ophthalmic solution 0.3%. [Prescribing information]. Fort Worth, TX; Novartis: March, 2017.

2. Ciloxan (ciprofloxacin) ophthalmic ointment 0.3%. [Prescribing information]. Fort Worth, TX; Novartis: February, 2017.

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.

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