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

Date:	May 7, 2019
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Product Name:	ZYMAR® (gatifloxacin ophthalmic solution) 0.3%
Pediatric Labeling Approval Date:	March 21, 2017
Application Type/Number:	NDA 021493
Applicant/Sponsor:	Allergan
OSE RCM #:	2019-590

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for ZYMAR® in pediatric patients through age 17 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA). This review focuses on serious unlabeled adverse events associated with ZYMAR® in pediatric patients.

The FDA approved ZYMAR® on March 28, 2003, for the treatment of bacterial conjunctivitis in adult and pediatric patients older than 1 year of age. The approved pediatric labeling on March 21, 2017, expanded the indication to pediatric patients less than 1 year of age.

DPV did not identify any pediatric safety concerns for ZYMAR® at this time and will continue to monitor all adverse events associated with its use.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for ZYMAR® in pediatric patients through age 17 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA). This review focuses on serious unlabeled adverse events associated with ZYMAR® in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

The FDA approved ZYMAR® (gatifloxacin ophthalmic solution) 0.3% on March 28, 2003, for the treatment of bacterial conjunctivitis caused by susceptible strains of *Haemophilus influenzae, Corynebacterium propinquum, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus mitis group,* and *Streptococcus pneumoniae* in adult and pediatric patients older than 1 year of age. The approved pediatric labeling on March 21, 2017, expanded the indication to pediatric patients less than 1 year of age.

The applicant conducted a single, adequate, and well-controlled clinical trial in subjects less than 1 month of age (birth to 31 days old) for the treatment of bacterial conjunctivitis, which compared ZYMAR® to moxifloxacin ophthalmic solution 0.5%. Clinical outcomes for the trial demonstrated clinical cure of 79% (44/56) for the ZYMAR®-treated group.

The Division of Transplant and Ophthalmology Products' clinical review included a review of all cases in the FAERS database from March 28, 2003, through March 2016, which found no significant safety issues, either in adults or in pediatric patients.

ZYMAR® has not been presented at a previous Pediatric Advisory Committee (PAC) meeting. However, ZYMAXID® (gatifloxacin ophthalmic solution) 0.5%, a higher strength formulation, was presented to the PAC on May 7, 2012. There were no safety reports in the pediatric population for ZYMAXID® and the Committee recommended a return to standard, ongoing monitoring for adverse events.

1.2 RELEVANT LABELED SAFETY INFORMATION[1]

_____CONTRAINDICATIONS_____

ZYMAR® solution is contraindicated in patients with a history of hypersensitivity to gatifloxacin, to other quinolones, or to any of the components in this medication.

_____WARNINGS AND PRECAUTIONS_____

- Hypersensitivity
- Growth of Resistant Organisms with Prolonged Use
- Corneal Endothelial Cell Injury

_____ADVERSE REACTIONS_____

Most common adverse reactions occurring in 5-10 % of patients included conjunctival irritation, increased lacrimation, keratitis, and papillary conjunctivitis.

_____PEDIATRIC USE _____

The safety and effectiveness of ZYMAR® (gatifloxacin ophthalmic solution) 0.3% have been established in all ages. Use of ZYMAR® is supported by evidence from adequate and well-controlled studies of ZYMAR® in adults, children and neonates.

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	March 12, 2019
Time Period of Search	April 1, 2016† - March 11, 2019
Search Type	Mercado Quick Search Drug Safety Analytics
Product Terms	Product Name – Zymar
MedDRA Search Terms (Version 21.1)	All Preferred Terms (PT)
* See Appendix A for a description of the FAERS database. † Date following medical officer's search of the FAERS database.	

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 April 1, 2016, through March 11, 2019, with ZYMAR®.

Table 2. Total Adult and Pediatric FAERS Reports Received by FDA from April 1, 2016, through March 11, 2019, with ZYMAR®			
	All reports (U.S.)	**Serious* (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	3 (1)	3 (1)	1 (1)
Pediatrics (0 - <17 years)	0 (0)	0 (0)	0 (0)
* 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.			

3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved zero U.S. serious pediatric cases from April 1, 2016, through March 11, 2019.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

We did not identify any fatal pediatric adverse event cases.

4 DISCUSSION

The FAERS database contained no reports for ZYMAR® in pediatric patients during the search period, and, therefore, we did not identify any safety signals.

5 CONCLUSION

DPV did not identify any pediatric safety concerns for ZYMAR® at this time.

6 RECOMMENDATION

DPV will continue to monitor all adverse events associated with the use of ZYMAR®.

7 REFERENCE

1. ZYMAR® [package insert]. Irvine, CA: Allergan; March 2017.

8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

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.

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