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Pediatric Postmarketing Pharmacovigilance

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Product Name: Vigamox (moxifloxacin hydrochloride ophthalmic solution 0.5%)

Pediatric Labeling Approval Date: March 14, 2017

Application Type/Number: NDA 21-598

Applicant/Sponsor: Alcon Inc.

OSE RCM #: 2019-592

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Vigamox (moxifloxacin hydrochloride ophthalmic solution 0.5%) in pediatric patients through age < 17 years of age. 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 U.S., serious adverse event reports associated with Vigamox in pediatric patients.

Vigamox was first approved on April 15, 2003 for the treatment of bacterial conjunctivitis caused by susceptible strains in patients aged 1 year and older. This review was prompted by the supplement approval for Vigamox on March 14, 2017 which expanded the indication to include patients less than 1 year of age. DPV has not presented Vigamox before the Pediatric Advisory Committee (PAC) in the past.

DPV reviewed the FDA Adverse Event Reporting System (FAERS) database for all U.S., serious reports with Vigamox in the pediatric population through age <17 years and identified seven nonfatal cases describing labeled adverse events of subconjunctival hemorrhage and hypersensitivity. There were no reports of death associated with Vigamox use in the pediatric population.

DPV identified no new safety signals and no increased severity of labeled adverse events in the pediatric population with Vigamox. DPV will continue to monitor adverse events associated with the use of Vigamox.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Vigamox (moxifloxacin hydrochloride ophthalmic solution 0.5%) in pediatric patients through age < 17 years of age. 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 U.S., serious adverse event reports associated with Vigamox in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Vigamox (moxifloxacin hydrochloride ophthalmic solution 0.5%) is supplied as a 4 mL bottle filled with 3 mL sterile ophthalmic solution of moxifloxacin in Alcon's DROP-TAINER® dispensing system. It is indicated in adults and all pediatric patients for the treatment of bacterial conjunctivitis caused by susceptible strains.¹

Vigamox was originally approved on April 15, 2003 under NDA 21-598 for patients aged 1 year and older. A supplement filed under NDA 21-598 expanded the indication for pediatric patients to less than 1 year of age. The supplement approval was supported by a randomized, controlled trial with Vigamox that included patients with bacterial conjunctivitis between birth and 31 days of age. At Day 9, there was an 80% clinical cure rate and a 92% microbiological eradication success rate for patients on Vigamox therapy.²⁻⁴

This review was prompted by the supplement approval for Vigamox to expand the indication for pediatric patients to less than 1 year of age. DPV has not presented Vigamox before the Pediatric Advisory Committee (PAC) in the past.

1.2 SELECTED LABELED SAFETY ISSUES

At the time of the March 2017 pediatric labeling change, the pertinent excerpted sections of the approved labeling for Vigamox were identical to the currently available package insert last updated December 2018:

-----CONTRAINDICATIONS-----

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

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

- Topical ophthalmic use only
- Hypersensitivity and anaphylaxis have been reported with systemic use of moxifloxacin
- Prolonged use may result in overgrowth of non-susceptible organisms, including fungi
- Patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis

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

The most frequently reported ocular adverse events were conjunctivitis, decreased visual acuity, dry eye, keratitis, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, subconjunctival hemorrhage, and tearing. These events occurred in approximately 1-6% of 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	March 20, 2019
Time Period of Search	April 15, 2003 [†] to March 19, 2019
Search Type	FBIS Quick Query
Product Terms	Product Name: Vigamox
MedDRA Search Terms (Version 21.1)	All adverse events
* See Appendix A for a description of the FAERS database.	
[†] U.S. approval date for Vigamox	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

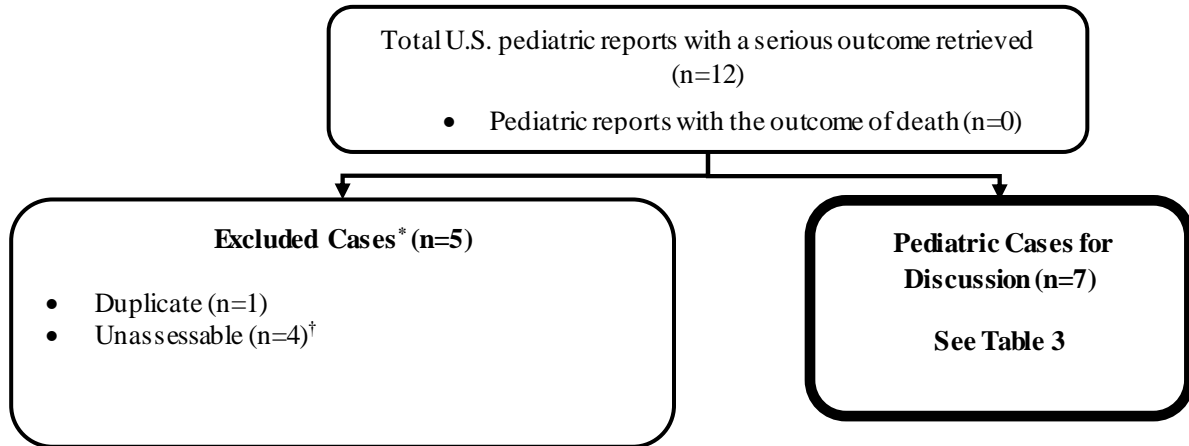
Table 2 presents the number of adult and pediatric FAERS reports from April 15, 2003 to March 19, 2019 with Vigamox.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA from April 15, 2003 to March 19, 2019 with Vigamox			
	All reports (U.S.)	Serious[†] (U.S.)	Death (U.S.)
Adults (> 17 years)	386 (261)	314 (192)	3 (3)
Pediatrics (0 - <17 years)	35 (20)	25 (12)	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.			

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

Our FAERS search retrieved 12 U.S. serious pediatric reports from April 15, 2003 to March 19, 2019 (see Table 2). We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded reports from the case series if the case was unassessable or a duplicate. After applying the exclusion criteria, seven cases remained for review. We summarize these seven cases in the sections below.

Figure 1. Selection of Serious U.S. Pediatric Cases with Vigamox



* DPV reviewed these cases, but they were excluded from further discussion for the reasons listed above

† Unassessable: Case cannot be assessed for causality (i.e., the case narrative only listed adverse events and did not have any other information; there was insufficient information to make an informed causality assessment)

3.1.3 Characteristics of Pediatric Cases

Appendix B contains a line listing of all pediatric cases.

Table 3 summarizes the seven FAERS cases in U.S. pediatric patients with Vigamox reporting a serious outcome received by FDA from April 15, 2003 to March 19, 2019.

Age	1 year	2
	3 years	1
	4 years	2
	6 years	1
	9 years	1
Sex	Male	3
	Female	4

^a The focus of this review is on U.S. serious adverse event reports, however, all U.S. pediatric reports of Vigamox were reviewed regardless of outcome. The U.S. non-serious reports retrieved in our FAERS cases did not reveal any specific patterns or trends suggestive of a safety concern at this time.

Table 3. Characteristics of the FAERS U.S. Serious Pediatric Cases with Vigamox Received by FDA from April 15, 2003 to March 19, 2019 (N=7)	
Reported Reason for Use	Bacterial Conjunctivitis 7
Reported Adverse Event*	Subconjunctival hemorrhage 4
	Hypersensitivity reaction 4
Serious Outcome†	Other Serious 7
* Cases may have reported more than one adverse event.	
† 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.	

3.1.4 Summary of Fatal Pediatric Cases (N=0)

We did not identify any fatal pediatric adverse event cases.

3.1.5 Summary of Non-Fatal Pediatric U.S. Serious Cases (N=7)

We identified seven FAERS cases with Vigamox in the U.S. pediatric population reporting a non-fatal serious outcome. In all seven cases, Vigamox was used for the FDA-approved indication of bacterial conjunctivitis, and all included AEs for labeled events of subconjunctival hemorrhage (n=4) and hypersensitivity reaction (n=4)^b; one case reported a subconjunctival hemorrhage and hypersensitivity reaction. These cases did not demonstrate a pattern of increased severity for the labeled adverse events.

4 DISCUSSION

There were no new safety signals identified for Vigamox in the pediatric population. There were no deaths reported and we identified no evidence of increased severity for the labeled adverse events with Vigamox in the pediatric population.

5 CONCLUSION

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

6 RECOMMENDATION

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

^b One case stated the patient experienced hypersensitivity but did not describe any symptoms. The remaining cases of hypersensitivity reported symptoms of urticaria (n=1), facial edema (n=2), and lacrimation (n=1). Cases may have reported more than one adverse event.

7 REFERENCES

1. Vigamox® (moxifloxacin hydrochloride ophthalmic solution 0.5%) [package insert]. Fort Worth, TX: Alcon Inc.; 2018.
2. U.S. Food & Drug Administration, New Pediatric Labeling Information Database. Available at: <https://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase> Accessed April 2019.
3. Clinical Review of NDA 21-598: Vigamox® (moxifloxacin ophthalmic solution) 0.5%. February 16, 2017. Available at: <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM553621.pdf>. Accessed April 2019.
4. Chambers, Wiley. Deputy Division Director Review of NDA 21-598. January 17, 2018. Available at: <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM553622.pdf>. Accessed April 2019.

8 APPENDICES

8.1 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 (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.

8.2 APPENDIX B. FAERS LINE LISTING OF U.S. PEDIATRIC CASE SERIES OF VIGAMOX WITH A SERIOUS OUTCOME (N=7)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age	Sex	Country Derived	Serious Outcomes*
1	2003-12-19	4048795 Duplicate case # 4060462	1	-	Direct	6.5 YR	Female	USA	OT
2	2006-04-14	6032235	1	-	Direct	4 YR	Female	USA	OT
3	2009-03-03	6935192	1	-	Direct	9 YR	Male	USA	OT
4	2009-11-06	7175618	1	-	Direct	4.15 YR	Male	USA	OT
5	2010-03-24	7336050	1	-	Direct	20 MTH	Female	USA	OT
6	2010-03-31	7356491	1	US-1181169	Expedited (15-Day)	1.46 YR	Male	USA	OT
7	2010-10-10	7666093	1	US-1183693	Expedited (15-Day)	3 YR	Female	USA	OT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events.

Abbreviations: YR = years, MTH = months, OT = Other serious medical event

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