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Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

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Product Name: Tetracaine Hydrochloride Ophthalmic Solution 0.5%

**Pediatric Labeling
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Application Type/Number: NDA 208135

Applicant/Sponsor: Alcon

OSE RCM #: 2018-501

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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 with a serious outcome for Tetracaine Hydrochloride Ophthalmic Solution 0.5% in pediatric patients.

Tetracaine Hydrochloride Ophthalmic Solution 0.5% was approved in 2016 and is supplied as single patient use, 4 mL filled in 4-mL plastic DROPTAINER[®] dispensers. It is indicated for use in adults and pediatric patients for procedures requiring a rapid and short-acting topical ophthalmic anesthetic.

A review of the FDA Adverse Event Reporting System (FAERS) database identified no new safety signals, no increased severity or frequency of any labeled adverse events, and there were no deaths reported in the pediatric population with Tetracaine Hydrochloride Ophthalmic Solution 0.5%.

There is no evidence from these data that there are new pediatric safety concerns with Tetracaine Hydrochloride Ophthalmic Solution 0.5% at this time.

We will continue to monitor adverse events associated with the use of Tetracaine Hydrochloride Ophthalmic Solution 0.5%.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Tetracaine Hydrochloride Ophthalmic Solution 0.5% was approved in 2016 and is supplied as single patient use, 4 mL filled in 4-mL plastic DROPTAINER® dispensers. It is indicated for use in adults and pediatric patients for procedures requiring a rapid and short-acting topical ophthalmic anesthetic.

Prior to approval, Tetracaine Hydrochloride Ophthalmic Solution had been sold in the United States for approximately 20 years. Tetracaine has been commercially available as an ophthalmic solution from several manufacturers in the United States for over 45 years for use as a topical anesthetic in ophthalmologic procedures. Previously, ophthalmic solutions of tetracaine had the status of “unapproved drug” by the U.S. Food and Drug Administration (FDA) and were being marketed and supplied in the United States without approved new drug applications. Consistent with FDA Guidance for FDA Staff and Industry entitled “Marketed Unapproved Drugs – Compliance Policy Guide: See 440.100 Marketed New Drugs Without Approved NDAs or ANDAs” dated September 19, 2011, Alcon submitted NDA 208135 as a 505(b)(2) application to help address this unapproved drug product being supplied and marketed as an unapproved product. The application relied on articles from the published literature, and no new efficacy studies were conducted by the applicant.

Per the Office of New Drugs Medical Officer’s review dated October 15, 2015, the reference data and postmarketing reporting confirm that tetracaine 0.5% is safe for use as a short-acting anesthetic. The adverse events associated with its use are non-serious and mostly related to the pain/discomfort felt on instillation of the drop.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

-----CONTRAINDICATIONS -----

- None

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

- Do not use intracamerally since use may damage corneal endothelial cells.
- Prolonged use or abuse may lead to corneal epithelial toxicity and may manifest as epithelial defects which may progress to permanent corneal damage.
- Patients should not touch the eye for at least 10-20 minutes after using anesthetic as accidental injuries can occur due to insensitivity of the eye.

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

Ocular adverse events: stinging, burning, conjunctival redness

----- **PEDIATRIC USE** -----

Safety in the pediatric population has been demonstrated in clinical trials. Efficacy of tetracaine hydrochloride ophthalmic solution for use in pediatric patients has been extrapolated from adequate and well controlled clinical trials in the adult population.

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 1. See Appendix A for a description of the FAERS database.

Table 1. FAERS Search Strategy

Date of Search	March 8, 2018
Time Period of Search	1969* through March 7, 2018
Search Type	Mercado Quick Search Drug Safety Analytics
Product Names	Product Active Ingredient – Tetracaine Tetracaine hydrochloride
Other Criteria	NDA 208135 Route of Administration [†] – Intracorneal Intraocular Ophthalmic Retробulbar Sunconjunctival (<i>sic</i>)
Search Parameters	All ages, all outcomes, worldwide

* Start of the FDA's adverse event database.

[†] All ocular routes of administration were included to account for possible differences in coding.

2.2 RESULTS

2.2.1 Total Number of FAERS Reports by Age

Table 2. Total Adult and Pediatric FAERS reports* through March 7, 2018, with Tetracaine Hydrochloride Ophthalmic Solution 0.5%

	All reports (U.S.)	Serious [†] (U.S.)	Death (U.S.)
Adults (≥ 17 years)	90 (62)	89 (61)	0 (0)
Pediatrics (0 - <17 years)	5 (4)	5 (4)	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.

2.2.2 Selection of Serious Pediatric Cases in FAERS

We identified five pediatric reports with a serious outcome (See Table 2). The one foreign report involved use of a tetracaine 1% solution, therefore, we excluded it as not relevant to the product under review.

2.2.3 Characteristics of Pediatric Case Series

Appendix B lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the Pediatric Case Series.

Table 3. Characteristics of Pediatric Case Series with Tetracaine Hydrochloride Ophthalmic Solution 0.5% (N=4)

Age	1 month - <2 years	4
Sex	Male	1
	Female	2
	Unknown	1
Country	United States	4
Reported Reason for Use	Retinopathy of prematurity (ROP) screening	4
Serious Outcome*	Hospitalization	1 [†]
	Other serious	3

** 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. Reports may have more than one outcome.*

[†] This case involved a premature neonate who was already hospitalized.

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 SERIOUS ADVERSE EVENT CASES (N=4)

All the reports were received prior to approval of NDA 208135, therefore, they may not refer to products identical to the approved drug.

In the four cases in which tetracaine was used for ROP screening, three cases noted the concomitant use of Cyclomydril eye drops, which is standard practice. The adverse events noted in these cases included bradycardia, apnea, and low oxygen saturation, which are unlabeled events. However, apnea and bradycardia of prematurity (ABP) is not rare in premature neonates. In addition, stress and pain, such as encountered during an ROP examination, are known to precipitate ABP.¹ Furthermore, the oculocardiac reflex from manipulation of the eye may cause apnea and bradycardia during the examination.² Therefore, the events are consistent with the underlying condition and procedure, and are unlikely related to the drug.

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 Tetracaine Hydrochloride Ophthalmic Solution 0.5%.

4 CONCLUSION

There is no evidence from these data that there are new pediatric safety concerns with Tetracaine Hydrochloride Ophthalmic Solution 0.5% at this time.

5 RECOMMENDATIONS

We will continue to monitor adverse events associated with the use of Tetracaine Hydrochloride Ophthalmic Solution 0.5%.

6 REFERENCES

1. Wood MG, Kaufman LM. Apnea and bradycardia in two premature infants during routine outpatient retinopathy of prematurity screening. *J AAPOS*. 2009 Oct;13(5):501-3.
2. Mitchell AJ, Green A, Jeffs DA, Roberson PK. Physiologic effects of retinopathy of prematurity screening examinations. *Adv Neonatal Care*. 2011 Aug;11(4):291-7.

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 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.

7.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES WITH TETRACAINE HYDROCHLORIDE OPHTHALMIC SOLUTION 0.5% (N=4)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (months)	Sex	Country Derived	Serious Outcomes*
1	21-May-2014	10186159	1	ALCN2014US 002934	EXPEDITED (15-DAY)	2	Female	USA	OT
2	06-Jun-2014	10223180	1		DIRECT	1	Female	USA	HO
3	06-Jun-2014	10223194	1		DIRECT	2	Male	USA	OT
4	31-Dec-2014	10687942	1		DIRECT	2	Unknown	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. This outcome should not be confused with the clinical outcome of the reported adverse drug experience. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A report may have more than one serious outcome.
Abbreviations: HO=Hospitalization, OT=Other medically significant

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/s/

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