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 and Drug Utilization Review

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Product Name:	Atropine Sulfate Ophthalmic Solution, USP 1%
Pediatric Labeling Approval Date:	July 18, 2014
Application Type/Number:	NDA 206289
Applicant/Sponsor:	Akorn, Inc.
OSE RCM #:	2017-428

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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 and drug utilization data for Atropine Sulfate Ophthalmic Solution, USP 1% in pediatric patients.

Atropine Sulfate Ophthalmic Solution, USP 1% was first approved in 2014 (although unapproved products have been used for over 100 years) and is indicated for cycloplegia, mydriasis, and penalization of the healthy eye in the treatment of amblyopia. The approved pediatric labeling is for cycloplegia, mydriasis, and penalization of the healthy eye in the treatment of amblyopia in individuals from 3 months of age or greater.

Drug utilization patterns were assessed in order to capture pediatric use of atropine sulfate ophthalmic solution 1% and to provide context for the adverse event reports submitted to the FDA Adverse Event Reporting System (FAERS) database for atropine sulfate ophthalmic solution 1%. From July 2014 through March 2017 a total of approximately 757,000 patients received a dispensed prescription for atropine sulfate ophthalmic solution 1% from U.S. outpatient retail pharmacies; of which, the pediatric population aged 0-16 years accounted for 15% (116,000 patients). Patients aged 3-16 years accounted for the largest proportion of pediatric use at 85% (98,000 patients) of pediatric patients. Although the data showed use in pediatric patients 2 years and younger, this use cannot be validated due to the lack of access to patient medical records.

Of the 23 reports reviewed in pediatric patients, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and the only death directly associated with atropine was the result of an unintentional overdose in which different formulations of atropine were administered to the patient.

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

We recommend a return to continuous pharmacovigilance monitoring.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Atropine Sulfate Ophthalmic Solution, USP 1% is available as an ophthalmic solution indicated for cycloplegia, mydriasis, and penalization of the healthy eye in the treatment of amblyopia.

Atropine ophthalmic solution has been used for pupilary dilation and cyclopegia for over 100 years. Previously, atropine ophthalmic solution products 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, Akorn submitted NDA 206289 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.

The original application for Atropine Sulfate Ophthalmic Solution, USP 1% included an assessment of the safety and effectiveness of the product for the claimed indications in pediatric patients as required under the Pediatric Research Equity Act (PREA). The Division of Transplant and Ophthalmology Products (DTOP) medical/clinical review included an adequate evaluation of the safety of atropine ophthalmic solution 1% in children greater than 3 months of age and in adults. At the time of approval, the Agency noted that Atropine Sulfate Ophthalmic Solution, USP 1% was appropriately labeled for use in all relevant pediatric populations.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

CONTRAINDICATIONS

Hypersensitivity or allergic reaction to any ingredient in formulation

WARNINGS AND PRECAUTIONS

- Photophobia and blurred vision due to pupil unresponsiveness and cycloplegia may last up to 2 weeks
- Risk of blood pressure increase from systemic absorption

ADVERSE REACTIONS

Most common adverse reactions that have been reported are eye pain and stinging on administration, blurred vision, photophobia, decreased lacrimation, increased heart rate and blood pressure

DRUG INTERACTIONS

The use of atropine and monoamine oxidase inhibitors (MAOI) is generally not recommended because of the potential to precipitate hypertensive crisis.

USE IN SPECIFIC POPULATIONS

Should only be used in pregnant women if clearly needed.

Due to the potential for systemic absorption of atropine sulfate ophthalmic solution, the use of atropine sulfate ophthalmic solution, USP 1% in children under the age of 3 months is not recommended and the use in children under 3 years of age should be limited to no more than one drop per eye per day.

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

Proprietary databases available to FDA were used to conduct the drug utilization analyses in this review. Detailed descriptions and limitations of the databases are included in Appendix A.

2.1.1 Data Sources Used

The QuintilesIMS National Sales Perspectives™ database was used to determine the settings of care where atropine sulfate ophthalmic solution 1% products were distributed by manufacturers to various U.S. distribution channels from July 2014 through March 2017.

The QuintilesIMS Total Patient Tracker™ (TPT) database was used to obtain the nationally estimated number of patients who received a dispensed prescription for atropine sulfate ophthalmic solution 1% from U.S. outpatient retail pharmacies, stratified by patient age groups (<1 year, 1-2 years, 3-16 years , and 17 years and older) from July 2014 through March 2017, aggregated.

2.2 RESULTS

2.2.1 Determining Settings of Care

According to sales distribution data from July 2014 through March 2017, approximately 63% of atropine sulfate ophthalmic solution 1% packages were distributed to U.S. non-retail settings of care (primarily long-term care facilities), 35% to outpatient retail pharmacies and 2% to mail order/specialty pharmacy settings.[1] Access to national estimates of patient data from long-term care facilities are not available to FDA at this time. Therefore, this drug utilization analysis focused on atropine sulfate ophthalmic solution use from only outpatient retail pharmacies. Data from mail-order/specialty and non-retail settings of care were not included in this analysis.

2.2.2 Number of Patients

Table 2.2.2

Nationally estimated number of patients who received a dispensed prescription for atropine sulfate ophthalmic solution 1% from U.S. outpatient retail pharmacies, stratified by patient age groups*, July 2014 to March 2017, aggregated

	July 2014 - March 2017	
	Patient Count‡ N	Share %
Total Patients	**757,076**	***100.0%***
0-16 years	**116,174**	***15.3%***
<1 year	**2,678**	***2.3%***
1-2 years	**17,672**	***15.2%***
3-16 years	**98,453**	***84.7%***
17 years and older	**628,609**	***83.0%***
Unspecified age	**6,637**	***0.9%***

***Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years of age (16 years and 11 months).**

‡Unique patient counts may not be added due to the possibility of double counting those patients aging during the study, and may be counted more than once in the individual categories.

Source: QuintilesIMS Total Patient Tracker. July 2014 - March 2017. Data extracted June 2017. File: TPT Enhanced 2017-428 Atropine Sulfate Oph Drops by Age 6-15-2017

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in Table 3.1.1. See Appendix B for a description of the FAERS database.

Table 3.1.1 FAERS Search Strategy

Date of Search	March 17, 2017
Time Period of Search	July 18, 2013* - as of date of search
Search Type	Product-Manufacturer Reporting Summary
Product Names	Product Active Ingredient – Atropine; Atropine sulfate
Search Parameters	All ages, all outcomes, worldwide
Filter	Route code – Ophthalmic

* Per OSE's Best Practices for Preparing Pediatric Postmarketing Pharmacovigilance and Drug Utilization Reviews, we used the date one year prior to the pediatric labeling change date as the start date for our FAERS search because the DTOP medical/clinical review included an adequate evaluation of the safety of atropine ophthalmic solution 1% in children greater than 3 months of age and in adults.

3.2 RESULTS

3.2.1 Total number of FAERS reports by Age

Table 3.2.1 Total Adult and Pediatric FAERS reports* from July 18, 2013, through March 16, 2017 with Atropine Sulfate Ophthalmic Solution, USP 1%

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	27 (9)	27 (9)	1 (0)
Pediatrics (0 - <17 years)	23 (1)	23 (1)	2 (1)

** 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.

3.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 23 pediatric cases with a serious outcome (See Table 3.2.1), which are summarized in **Sections 3.3 and 3.4.**

3.2.3 Characteristics of Pediatric Case Series

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

Table 3.2.3 Characteristics of Pediatric Case Series with Atropine Sulfate Ophthalmic Solution (N=23)

Age (n=23)	0 - < 1 month	2
	1 month - <2 years	10
	2- < 6 years	8
	6- <12 years	2
	12- < 17 years	1
Sex	Male	10
	Female	13
Country	United States	1
	Foreign	22
Reported Reason for Use (some reports included more than one)	Ophthalmologic exam	11
	Mydriasis	3
	Strabismus	2
	Amblyopia	1
	Corneal perforation	1
	Cycloplegia	1
	Fundoscopy	1
	Iridocyclitis	1
	Pre-operative	1
	Unknown	3
Serious Outcome*	Death	2
	Life-threatening	1
	Hospitalization	9
	Disability	1
	Other serious	12

* 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.

3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=2)

- Two cases reported death as an outcome.

- One of the cases was from France and involved a 13-month-old male in which the death was not directly associated with the drug (case # 11702983). Atropine 0.3% had been given at a dose of one drop in both eyes twice a day for a total of 5 days for the treatment of strabismus. The patient had Down's syndrome (Trisomy 21), and multiple medical problems including an atrioventricular septal defect, which was surgically repaired, cardiac decompensation complicated with pneumopathy, respiratory decompensation, hypothyroiditis, and required enteral nutrition. After being hospitalized for acute febrile respiratory distress, the patient developed encephalopathy and died following three cardiorespiratory arrests. Septic shock, meningoencephalitis, and "malignant hyperthermia on a sepsis" were considered as possible causes of death.

- The second case was a literature report from 1939 describing atropine intoxication in infants and children (case # 12386096). A 3-year-old female was admitted with a perforated cornea. Pre-operatively she was administered 6 drops of atropine 1% into the eye and given 0.1 mg of atropine subcutaneously. Post-operatively, a dressing containing 1.5 grams of atropine 1% ointment was placed next to the eye. The patient developed atropine intoxication with tachycardia, fever, restlessness, labored breathing and eventually expired. The total amount of atropine administered was 18.1 mg.

  Reviewer's comment: This case describes an unintentional overdose. The product labeling notes that in pediatric populations, 10 mg or less may be fatal.

3.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=21)

All of the 21 non-fatal serious cases came from foreign sources. The prescribing practices in other countries may differ from those in the United States. For example, several cases described atropine doses of one drop twice a day in patients less than 3 years of age, whereas the U.S. prescribing information recommends limiting atropine to no more than one drop per eye per day in children under 3 years of age.

The adverse events reported in these cases represented known, labeled events typically associated with atropine's anticholinergic pharmacologic properties, including restlessness and irritability from stimulation of the central nervous system (i.e., agitation), flushing, tachycardia, and pyrexia. The most frequently reported MedDRA Preferred Terms occurred in no more frequently than four cases and also included mydriasis and drug dispensing errors/incorrect dose administered. Of the eight hospitalizations related to the use of atropine (one case involved

pilocarpine), the cases typically involved parents taking their children to the emergency room secondary to the effects of atropine such as tachycardia and agitation in which they were admitted for observation. There were no new risks, or known/labeled risks reported in unusual numbers.

4 DISCUSSION

Of the 23 cases reviewed in pediatric patients, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and the only death directly associated with atropine was the result of an unintentional overdose in which different formulations of atropine were administered to the patient.

Analysis of drug utilization data showed that pediatric patients aged 0-16 years old accounted for 15% (116,000 patients) of total patients who received a dispensed prescription for atropine sulfate ophthalmic solution 1% from U.S. outpatient retail pharmacies from July 2014 through March 2017. Among pediatric patients 16 years or younger, the largest proportion of atropine sulfate ophthalmic solution 1% use was seen in patients aged 3-16 years. Although use in pediatric patients 2 years and younger were captured, this use cannot be validated due to lack of access to patient medical records. Furthermore, our analysis only focused on the outpatient retail setting and might not apply to other settings of care such as long-term care, hospitals and clinics where atropine sulfate ophthalmic solution may be used. Therefore, our results may underestimate patient utilization.

5 CONCLUSION

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

6 RECOMMENDATIONS

Return to continuous pharmacovigilance monitoring.

7 REFERENCES

1. QuintilesIMS National Sales Perspectives™. July 2014 – March 2017. Extracted June 2017. File: NSP 2017-428 Atropine Sulfate Oph Drops by Sup Ch 6-15-2017.xlsx.

8 APPENDICES

8.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

QuintilesIMS, National Sales Perspectives

The QuintilesIMS, National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

QuintilesIMS, Total Patient Tracker

The QuintilesIMS, Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 2.1 billion prescription claims per year.

8.2 APPENDIX B. 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.

8.3 APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH ATROPINE SULFATE OPHTHALMIC SOLUTION (N=23)

FAERS Case #	Version #	Manufacturer Control #
10219814	2	ALCN2014MY003231
10258609	2	ALCN2014FR003610
10377279	1	ALCN2014BE004463
10561566	1	ALCN2014FR006066
10591627	2	ALCN2014FR006322
10596432	1	ALCN2014BE006404
10724973	2	ALCN2015FR000614
10727935	1	ALCN2015SE000691
11184870	1	ALCN2015FR003665
11491969	1	ALCN2015FR005571
11702983	1	ALCN2015FR006702
11887477	5	ALCN2015ES008003
11898475	1	ALCN2015FR008140
12165652	1	ALCN2016FR001044
12172629	1	ALCN2015FR005058
12172993	1	ALCN2016FR001701
12386096	1	US-PFIZER INC-2016227550
12538213	1	ALCN2016FR004577
12563395	1	ALCN2016FR004699
9464299	3	ALCN2013FR004143
9562886	2	ALCN2013FR004840
9833581	2	ALCN2014FR000521
9886734	1	ALCN2014FR000995

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/s/

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08/04/2017

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08/06/2017
The drug use data in this review has been cleared by the database vendor

JUSTIN A MATHEW
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