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:	Latisse® (bimatoprost ophthalmic solution) 0.03%
Pediatric Labeling Approval Date:	September 4, 2014
Application Type/Number:	NDA 022369
Applicant/Sponsor:	Allergan
OSE RCM #:	2017-115

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) and the 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 Latisse® (bimatoprost ophthalmic solution) 0.03% in pediatric patients.

Latisse® (bimatoprost ophthalmic solution) 0.03% was first approved in 2008 and is indicated for the treatment of hypotrichosis of the eyelashes. At the time of approval, the safety and efficacy of bimatoprost in pediatric patients had not been studied. The original approval letter for Latisse® included a requirement for a pediatric study under PREA in pediatric patients 0 to 17 years of age.

Drug utilization patterns were assessed in order to capture pediatric use of bimatoprost and to provide context for the adverse event reports submitted to the FDA Adverse Event Reporting System (FAERS) database. During the examined time period, pediatric patients ages 0-16 years accounted for less than 1% (925 patients) of the total patients with a prescription claim from a U.S. outpatient retail pharmacy for brand or generic Latisse® (bimatoprost) 0.03% ophthalmic products. Among the pediatric patients, the majority (75%, 693 patients) of patients were ages 12-16 years.

The only serious case reported was unrelated to Latisse® as the medication was used by a pregnant female at the beginning of her pregnancy in which the newborn was delivered prematurely, developed a bacterial infection, and subsequently died.

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

We recommend a return to routine pharmacovigilance.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Latisse® 0.03% is available as an ophthalmic solution indicated for the treatment of hypotrichosis of the eyelashes by increasing their growth, including length, thickness and darkness.

Studies of Latisse® in pediatric patients were not conducted as part of the original NDA and were deferred under PREA because the application was otherwise ready for approval in adults. Use of Latisse® was subsequently evaluated in a sixteen week double-masked, randomized, vehicle-controlled study conducted in pediatric patients 5 to 17 years of age who were post-chemotherapy or had alopecia areata, and adolescents 15 to 17 years of age who had hypotrichosis with no associated medical condition. No new safety issues were observed. Studies in pediatric patients less than 5 years of age were waived because such studies were considered to be impossible or highly impractical. The sponsor submitted the results of the study on March 4, 2014, with subsequent approval and labeling on September 4, 2014.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

_____CONTRAINDICATIONS_____

None

_____WARNINGS AND PRECAUTIONS_____

Concurrent administration of LATISSE® and IOP-lowering prostaglandin analogs in ocular hypertensive patients may decrease the IOP-lowering effect. Patients using these products concomitantly should be closely monitored for changes to their intraocular pressure.

Pigmentation of the eyelids and iris may occur. Iris pigmentation is likely to be permanent.

_____ADVERSE REACTIONS_____

Most common adverse reactions (incidence approximately 3% -4%) are eye pruritus, conjunctival hyperemia, and skin hyperpigmentation.

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

We used proprietary drug utilization databases available to FDA to conduct this analysis. Detailed database descriptions are provided in Appendix A.

2.1.1 Data Sources Used

The QuintilesIMS, National Sales Perspectives™ (NSP) was used to determine the settings of care where bottles or packages of brand and generic Latisse® (bimatoprost)0.03% topical ophthalmic solution were distributed from the manufacturers in 2016.

The Symphony Health Solutions' Integrated Dataverse (IDV)™ database was used to obtain the nationally estimated number of patients with a prescription claim for Latisse® (brand and generic) bimatoprost 0.03% topical ophthalmic solution from U.S. retail outpatient pharmacies, stratified by patient age (0-4 years, 5-11, 12-16, and 17 years and older) from February 1, 2014, through January 31, 2017, aggregated.

2.2 RESULTS

2.2.1 Settings of Care

According to sales distribution data in 2016, 69% of brand and generic Latisse® (bimatoprost) 0.03% products were distributed to non-retail settings of care (primarily to clinics), followed by 31% to outpatient retail pharmacies, and less than 1% to mail-order/specialty pharmacy settings. National estimates of utilization for brand and generic Latisse® in non-retail settings, such as clinics, were not available. Therefore, this analysis provides national estimates of patients based on dispensed prescription data for the U.S. outpatient retail pharmacy setting; *prescription claims* were captured using the National Drug Codes (NDCs) for brand and generic Latisse®.

2.2.2 Patient Level Data

Table 2.2.2. Nationally Estimated Number of Patients with a Prescription Claim* for Latisse® (brand or generic) Bimatoprost 0.03% Topical Ophthalmic Solution, Stratified by Patient Age, February 1, 2014 - January 31, 2017, Aggregated

	February 2014 - January 2017	
	Patients (N)	*Share (%)*
Total Patients (age)**	272,764	*100.0%*
Age 0-16 years	925	*0.3%*
0-4 years	34	3.7%
5-11 years	199	21.5%
12-16 years	693	74.9%
Age 17 + years	271,829	*99.7%*
Age unknown	14	*<0.1%*

Source: Symphony Health Solutions' Integrated Dataverse (IDV)™. Feb 2014 - Jan 2017. Extracted May 2017
File: SHSCPA 2017-115 Latisse BPCA May 22 2017.xlsx

* Claims are from U.S. commercial, Medicare Part D, Cash, and Medicaid plans; data includes patients with prescription claims based on National Drug Code (NDC).

**Age is at first claim during study period.

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	February 6, 2017
Time Period of Search	December 24, 2008* - January 31, 2017
Search Type	Product-Manufacturer Reporting Summary
Product Names	Product Name – Latisse Product Verbatims – Bimatoprost 0.03%; Bimatoprost 0.03% Oph Soln; Bimatoprost 0.03% Sol Eye; Bimatoprost 0.03% Sol-Eye (9106X); Bimatoprost 0.03% Sol UD-Eye (10037X); Bimatoprost 0.03% Sol-Eye (9106X); Bimatoprost 0.03% Sol-Skin (11074X); Bimatoprost 0.03% Sol-Skin (9106X); Bimatoprost Ophthalmic .03% Allergan, Inc; Bimatoprost Ophthalmic Solution 0.3 %; Latisse (Bimatoprost Opthalmic 0.03%-3 ml Allergan; Latisse (Bimatoprost); Latisse 0.03% (Bimatoprost) (Bimatoprost); Latisse 0.03% Bimatoprost; Latisse 0.03% Bimatoprost 0.3 mg/ml Allergan; Latisse 0.03% Bimatoprost Allergan, Ophthalmic Sol 0023-3616-036 NDC; Latisse 0.03% Bimatoprost Ophthalmic Sol Allergan, Inc / NDC 0023-3616-03; Latisse Bimatoprost 0.03% Allergan; Latisse Bimatoprost Ophthalmic Allergan; Latisse Bimatoprost Ophthalmic Solution Allergan, Inc Irvine, CA 92612; Latisse-Bimatoprost- 0.03% Allergan; Latisse/Bimatoprost Opthalmic Solutions .08; Lattise - Bimatoprost 0.03% Allergan
NDA #	022369
Search Parameters	All ages, all outcomes, worldwide

* *U.S. Approval date*

3.2 RESULTS

3.2.1 Total number of FAERS reports by Age

Table 3.2.1 Total adult and pediatric FAERS reports* from December 24, 2008, through January 31, 2017, with bimatoprost ophthalmic solution 0.03%

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	3828 (3800)	147 (123)	2 (0)
Pediatrics (0 to <17)	6 (6)	1 (1)	1 (1)

**** May include duplicates and transplacental exposures; reports 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 one pediatric report with a serious outcome (See Table 3.2.1).

3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASE (N=1)

FAERS Case Number 8381330, Version Number 1, Manufacturer Control Number US-ALLERGAN-1201125US—A spontaneous report was received from a mother regarding a neonate who experienced a bacterial infection and a premature birth following the mother's administration of LATISSE 0.03% (bimatoprost) during the first 2 weeks of her pregnancy. LATISSE 0.03% was started by the mother in February 2011 (dose regimen of 1 drop applied topically to each upper lid eyelash margin). The mother discontinued use of LATISSE in (b) (6) upon finding that she was 2 weeks pregnant. The patient was hospitalized four months later as her water broke early and delivered the patient six days later (delivery type unknown) at 23.4 weeks gestation. The mother reported that the patient developed a bacterial infection, lived for 1 hour and passed away (details unknown). The mother also used Eyeliner and Mascara concomitantly with LATISSE. No medical history was reported for the mother nor the patient in this case.

4 DISCUSSION

During the examined time period, a nationally estimated number of 272,764 patients were captured with a prescription claim for brand or generic Latisse® (bimatoprost) 0.03% ophthalmic solution from U.S. outpatient retail pharmacies. Pediatric patients aged 0-16 years accounted for less than 1% (925 patients) of patients, the majority of which (75%, 693 patients) were patients 12-16 years of age. It is important to note that the data provided are based on dispensed

prescription claims, these data do not undergo chart validation for accuracy of abstracted information, such as date of birth, from prescription level data.

The FAERS review did not identify any new safety signals, no increased severity or frequency of any labeled adverse events, and there were no deaths directly associated with Latisse® in pediatric patients. The only serious case reported was unrelated as the medication was used by a pregnant female at the beginning of her pregnancy in which the newborn was delivered prematurely, developed a bacterial infection, and subsequently died.

5 CONCLUSION

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

6 RECOMMENDATIONS

Return to routine pharmacovigilance monitoring.

7 APPENDICES

7.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

National Sales Perspectives (NSP)

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.

Symphony Health Solutions' IDV® (Integrated Dataverse)

Symphony Health Solutions' IDV (Integrated Dataverse) contains longitudinal patient data sources that capture adjudicated prescription, medical, and hospital claims across the United States for all payment types, including commercial plans, Medicare Part D, cash, assistance programs, and Medicaid. The IDV contains over 10 billion prescriptions claims linked to over 220 million unique prescription patients of with an average of 4.2 years of prescription drug history. Claims from hospital and physician practices include over 190 million patients with CPT/HCPCS medical procedure history as well as ICD-9 diagnosis history of which nearly 140 million prescription drug patients are linked to a diagnosis. The overall sample represents over 54,000 pharmacies, 1,500 hospitals, 800 outpatient facilities, and 80,000 physician practices.

7.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

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.

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/s/

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