**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Surveillance and Epidemiology**
**Office of Pharmacovigilance and Epidemiology**

# Pediatric Postmarketing Pharmacovigilance Review

| | |
|---|---|
| **Date:** | December 21, 2023 |
| **Reviewers:** | Omayma Kishk, PharmD, BCPPS, Safety Evaluator<br>Division of Pharmacovigilance-I (DPV-I)<br><br>Ivone Kim, MD, Medical Officer<br>DPV-I |
| **Team Leader:** | Carmen Cheng, PharmD<br>DPV-I |
| **Division Director:** | Monica Muñoz, PharmD, PhD, BCPS<br>DPV-I |
| **Product Name:** | Lotemax (loteprednol etabonate ophthalmic gel) 0.5% |
| **Pediatric Labeling Approval Date:** | July 20, 2018 |
| **Application Type/Number:** | NDA 202872 |
| **Applicant:** | Bausch and Lomb Inc. |
| **TTT Record ID:** | 2023-6310 |

**TABLE OF CONTENTS**

## EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for loteprednol etabonate in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with loteprednol etabonate in pediatric patients.

Lotemax (loteprednol etabonate ophthalmic gel) 0.5% (NDA 202872) is a corticosteroid and was initially approved in the U.S. on September 28, 2012. Loteprednol etabonate is available in various dosage strengths and dosage forms. Loteprednol etabonate ophthalmic gel and ointment are currently indicated for the treatment of postoperative inflammation and pain following ocular surgery.

This pediatric postmarketing safety review was stimulated by the pediatric labeling for loteprednol etabonate ophthalmic gel 0.5% on July 20, 2018, that expanded the indication for use in pediatric patients aged from birth to 11 years. A pediatric safety review for loteprednol etabonate has not previously been presented to the Pediatric Advisory Committee.

DPV reviewed all U.S. serious FAERS reports with loteprednol etabonate in pediatric patients less than 17 years of age from September 28, 2012 to October 31, 2023, and identified one report; however, the report was excluded from further discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with loteprednol etabonate in pediatric patients less than 17 years of age.

# 1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for loteprednol etabonate in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with loteprednol etabonate in pediatric patients.

## 1.1 PEDIATRIC REGULATORY HISTORY

Lotemax (loteprednol etabonate ophthalmic gel) 0.5% (NDA 202872) is a corticosteroid and was initially approved in the U.S. on September 28, 2012. Loteprednol etabonate is available in various dosage strengths and dosage forms. Loteprednol etabonate ophthalmic gel and ointment are currently indicated for the treatment of postoperative inflammation and pain following ocular surgery.[1] See Table 1 for the currently available loteprednol etabonate products, including the drug name, application number, dosage strength and form, initial FDA approval date, use in pediatric population, and indication.

**Table 1. Approved Loteprednol Etabonate Products**

| Drug Name/ New Drug Application (NDA) Number | Dosage Strength and Form | FDA Approval Date | Approved in Pediatric Population |
|---|---|---|---|
| Lotemax/ NDA 20583[2] | 0.5% ophthalmic suspension/drops | March 9, 1998* | No |
| Alrex/ NDA 20803[3] | 0.2% ophthalmic suspension/drops | March 9, 1998† | No |
| Lotemax/ NDA 200738[4] | 0.5% ophthalmic ointment | April 15, 2011 | No |
| Lotemax/ NDA 202872[1] | 0.5% ophthalmic gel | September 28, 2012 | Yes |
| Inveltys/ NDA 210565[5] | 1% ophthalmic suspension | August 22, 2018 | No |
| Lotemax SM/ NDA 208219[6] | 0.38% ophthalmic gel | February 22, 2019 | No |
| Eysuvis/ NDA 210933[7] | 0.25% ophthalmic suspension/drops | October 26, 2020‡ | No |

* Indicated for 1) treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitides, when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation; and 2) treatment of postoperative inflammation and pain following ocular surgery.
† Indicated for the temporary relief of the signs and symptoms of seasonal allergic conjunctivitis.
‡ Indicated for the short-term (up to two weeks) treatment of the signs and symptoms of dry eye disease.

This pediatric postmarketing safety review was stimulated by the pediatric labeling for loteprednol etabonate ophthalmic gel 0.5% on July 20, 2018, that expanded the indication for use in pediatric patients aged from birth to 11 years.[8]

A pediatric safety review for loteprednol etabonate has not previously been presented to the Pediatric Advisory Committee.

### 1.2 RELEVANT LABELED SAFETY INFORMATION

The loteprednol etabonate ophthalmic gel 0.5% labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional loteprednol etabonate ophthalmic gel 0.5% labeling information, please refer to the full prescribing information.[1]

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

- Intraocular pressure (IOP) increase - Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. If this product is used for 10 days or longer, IOP should be monitored. (5.1)
- Cataracts - Use of corticosteroids may result in posterior subcapsular cataract formation. (5.2)
- Delayed healing – The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining. (5.3)
- Bacterial infections – Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infection. In acute purulent conditions, steroids may mask infection or enhance existing infection. (5.4)
- Viral infections – Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). (5.5)
- Fungal infections – Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. (5.6)

---------- **ADVERSE REACTIONS** ----------

The most common adverse drug reactions (2-5%) were anterior chamber inflammation, eye pain, and foreign body sensation. (6)

**8.4 Pediatric Use**

The safety and effectiveness of LOTEMAX have been established in the pediatric population. Use of LOTEMAX in this population is supported by evidence from adequate and well-controlled trials of LOTEMAX in adults with additional data from a safety and efficacy trial in pediatric patients from birth to 11 years of age *[see Clinical Studies (14)]*.

## 2 METHODS AND MATERIALS

### 2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 2.

| Table 2. FAERS Search Strategy* | |
|---|---|
| Date of search | November 1, 2023 |
| Time period of search | September 28, 2012† - October 31, 2023 |
| Search type | RxLogix Pediatric Focused Review Alert – DPV |
| Product terms | Product Active Ingredient: Loteprednol, Loteprednol Etabonate |
| MedDRA search terms (Version 26.0) | All Preferred Terms |

* See Appendix A for a description of the FAERS database.
† U.S. approval date of loteprednol etabonate) ophthalmic gel 0.5%
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities

# 3 RESULTS

## 3.1 FAERS

### *3.1.1 Total Number of FAERS Reports by Age*

Table 3 presents the number of adult and pediatric FAERS reports from September 28, 2012 to October 31, 2023, with loteprednol etabonate.

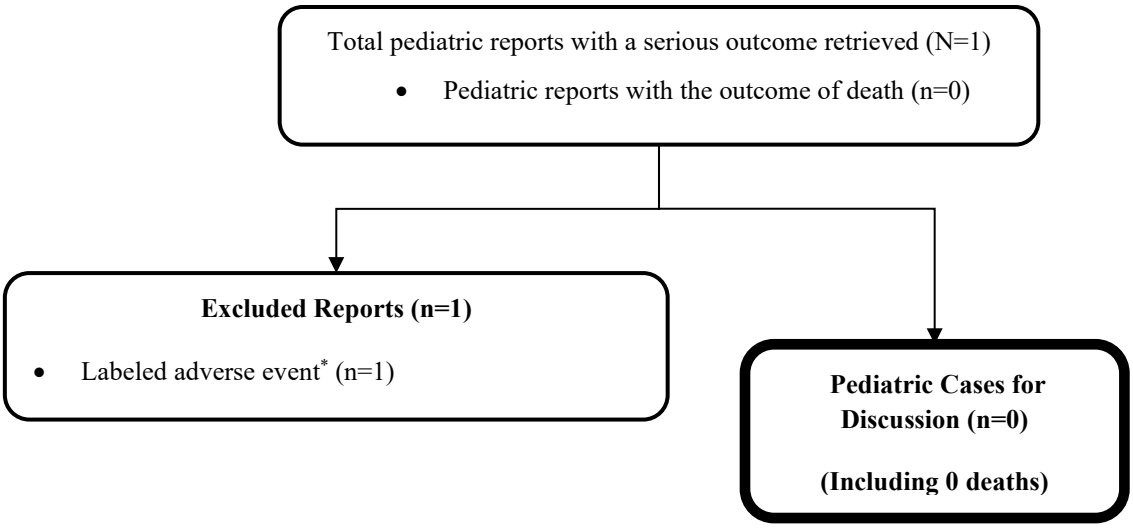
| Table 3. Total Adult and Pediatric FAERS Reports* Received by FDA From September 28, 2012 to October 31, 2023 With Loteprednol Etabonate | | | |
|---|---|---|---|
| | **All Reports (U.S.)** | **Serious† (U.S.)** | **Death (U.S.)** |
| Adults (≥ 17 years) | 963 (883) | 266 (192) | 3 (3) |
| Pediatrics (0 - < 17 years) | 11 (4) | 8 (1) | 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, or other serious important medical events.

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

Our FAERS search retrieved one U.S. serious pediatric report from September 28, 2012 to October 31, 2023. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded one report from the case series for the reasons listed in Figure 1. Figure 1 presents the selection of cases for the pediatric case series.

**Figure 1. Selection of U.S. Serious Pediatric Cases With Loteprednol Etabonate**




* Labeled adverse event does not represent increased severity or frequency.

#### *3.1.3 Summary of U.S. Fatal Pediatric Cases (N=0)*

There are no fatal pediatric adverse event cases for discussion.

#### *3.1.4 Summary of U.S. Serious Non-Fatal Pediatric Cases (N=0)*

There are no non-fatal pediatric adverse event cases for discussion.

## 4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with loteprednol etabonate in pediatric patients less than 17 years of age from September 28, 2012 to October 31, 2023, and identified one report; however, the report was excluded from further discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with loteprednol etabonate in pediatric patients less than 17 years of age.

## 5 CONCLUSION

DPV did not identify any new pediatric safety concerns for loteprednol etabonate at this time and will continue routine pharmacovigilance monitoring for loteprednol etabonate.

## 6 REFERENCES


1. Lotemax (loteprednol etabonate ophthalmic gel) 0.5%, for topical ophthalmic use [Prescribing Information]. Bridgewater, NJ: Bausch & Lomb Incorporated; July 2018.
2. Lotemax (loteprednol etabonate ophthalmic suspension) 0.5%, for topical ophthalmic use [Prescribing Information]. Tampa, FL: Bausch & Lomb Pharmaceuticals, Inc.; March 1998.
3. Alrex (loteprednol etabonate ophthalmic suspension) 0.2%, for topical ophthalmic use [Prescribing Information]. Tampa, FL: Bausch & Lomb Pharmaceuticals, Inc.; March 1998.
4. Lotemax (loteprednol etabonate ophthalmic ointment) 0.5%, for topical ophthalmic use [Prescribing Information]. Bridgewater, NJ: Bausch & Lomb Incorporated; December 2020.
5. Inveltys (loteprednol etabonate ophthalmic suspension) 1%, for topical ophthalmic use [Prescribing Information]. Watertown, MA: Kala Pharmaceuticals, Inc.; April 2020.
6. Lotemax SM (loteprednol etabonate ophthalmic gel) 0.38%, for topical ophthalmic use [Prescribing Information]. Bridgewater, NJ: Bausch & Lomb Incorporated; February 2019.
7. Eysuvis (loteprednol etabonate ophthalmic suspension) 0.25%, for topical ophthalmic use [Prescribing Information]. Watertown, MA: Kala Pharmaceuticals, Inc.; October 2020.
8. Lim L. Clinical Review of NDA 202872/S-002 Lotemax (lotepredenol etabonate) ophthalmic gel 0.5%. March 2018. https://www.fda.gov/media/115464/download.

# 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 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 terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

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 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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