**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 Review

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Product Name: Kovanaze (tetracaine HCl and oxymetazoline HCl)
                                               Nasal Spray

**Pediatric Labeling
Approval Date:**   June 29, 2016

Application Type/Number: NDA 208032

Sponsor: St. Renatus LLC

OSE RCM #:   2018-1178

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EXECUTIVE SUMMARY

In accordance with the Pediatric Research Equity Act (PREA), the Division of Pharmacovigilance (DPV) evaluated postmarketing adverse event reports with a serious outcome for Kovanaze (tetracaine HCl and oxymetazoline HCl) nasal spray in pediatric patients.

Kovanaze (tetracaine HCl and oxymetazoline HCl) nasal spray was first approved on June 29, 2016 and is indicated for regional anesthesia when performing a restorative procedure on Teeth 4-13 and A-J in adults and children who weigh 40 kg or more.

There are currently no cases in the FDA Adverse Event Reporting System (FAERS) in pediatric patients for Kovanaze. There is no evidence from these data that there are pediatric safety concerns with Kovanaze at this time. The Division of Pharmacovigilance II will continue routine pharmacovigilance monitoring of the FAERS database for cases reported in the pediatric population with Kovanaze.

1   INTRODUCTION

Kovanaze (tetracaine HCl and oxymetazoline HCl) is available as a pre-filled, single-use intranasal sprayer. Each nasal spray delivers 0.2 mL containing 6 mg tetracaine hydrochloride and 0.1 mg oxymetazoline hydrochloride. Kovanaze is indicated for regional anesthesia when performing a restorative procedure on Teeth 4-13 and A-J[a] in adults and children who weigh 40 kg or more.

1.1 PEDIATRIC REGULATORY HISTORY

The original Kovanaze (NDA 208032, St. Renatus LLC) approval on June 29, 2016 included use in pediatric patients who weigh ≥40 kg. The Sponsor conducted a multicenter-randomized, double blind placebo-controlled trial in pediatric patients between 3 and 17 years old. The pediatric patients were further stratified into three weight range categories: 10 to <20 kg, 20 to <40 kg, and ≥40 kg. The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) review of this study found that "although the results in the 20 to <40 kg dosage strata demonstrated a numerical difference in favor of the Kovanaze treatment group, the results were not statistically significant." Therefore, DAAAP approved Kovanaze only in children who weigh ≥40 kg. This study satisfied the PREA requirement and therefore, *the pediatric labeling and approval date are the same*. The Kovanaze Label Changes Summary from the New Pediatric Labeling Information Database is in Appendix A.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

CONTRAINDICATIONS

Known hypersensitivity to tetracaine, benzyl alcohol, other ester local anesthetics, *p*-aminobenzoic acid (PABA), oxymetazoline, or any other component of the product.

WARNINGS AND PRECAUTIONS

Hypertension and Thyroid Disease: Shown to increase blood pressure in some clinical trial patients. Monitor blood pressure. Use in patients with inadequately controlled hypertension or active thyroid disease is not advised.

Epistaxis: Use is not recommended in patients with a history of frequent nose bleeds (≥5 per month). If a decision to use is made, monitor these patients carefully.

Dysphagia: Carefully monitor patients for dysphagia

Methemoglobinemia: May cause methemoglobinemia, particularly when used with methemoglobin-inducing agents. Use in patients with history of congenital or idiopathic methemoglobinemia not advised. If central cyanosis unresponsive to oxygen therapy occurs, suspect methemoglobinemia, confirm diagnosis with co-oximetry, and treat with a standard clinical regimen.

Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs.

ADVERSE REACTIONS

The most common adverse reactions occurring in >10% of patients include rhinorrhea, nasal congestion, lacrimation increased, nasal discomfort, and oropharyngeal pain.

Transient, asymptomatic elevations in systolic blood pressure (≥ 25 mm Hg from baseline) and diastolic blood pressures (≥ 15 mm Hg from baseline) have been reported.

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[a]A-J are the Primary ('baby') maxillary teeth; 4-13 are the permanent ('adult') maxillary teeth excluding molars.

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DRUG INTERACTIONS

Monoamine oxidase inhibitors (MAOIs): Concomitant use of MAOIs, nonselective beta adrenergic antagonists, or tricyclic antidepressants may cause hypertension and is not recommended

Oxymetazoline-containing products: Discontinue use 24 hours prior to KOVANAZE administration.

Intranasal products: Avoid concomitant use.

2   POSTMARKET ADVERSE EVENT REPORTS

2.1   METHODS AND MATERIALS

2.1.1   FAERS Search Strategy

DPV-II searched the FAERS database with the strategy described in Table 1. See Appendix B for a description of the FAERS database.

Table 1. FAERS Search Strategy	
Date of Search	May 29, 2018
Time Period of Search	Entire database as of April 30, 2018
Search Type	Quick Query
Drug Name(s)	*Product Active Ingredient:* Oxymetazoline\ Tetracaine; Oxymetazoline Hydrochloride\Tetracaine Hydrochloride *Product Name*: Kovanaze *Product Verbatim Name*: Kovanaze
Search Parameters	All ages, all outcomes, worldwide NDA 208032

2.2   RESULTS

2.2.1   Total number of FAERS reports by Age

Table 2. Total Adult and Pediatric FAERS Reports[*] as of April 30, 2018 with Kovanaze (tetracaine HCl and oxymetazoline HCl) intranasal spray

	All reports (US)	Serious[†] (US)	Death (US)
Adults (≥17 years)	26 (26)	4(4)	0 (0)
Pediatrics (0 - <17 years)	0 (0)	0 (0)	0[‡] (0)

[*]*May include duplicates 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.*
[‡]*No reports of pediatric deaths were identified among reports not reporting an age.*

Reference ID: 4295582

3   DISCUSSION

There were no reports for Kovanaze in pediatric patients, and, therefore, no safety signals were identified.

4   CONCLUSION

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

5   RECOMMENDATIONS

The Division of Pharmacovigilance II will continue routine pharmacovigilance monitoring of the FAERS database for cases reported in the pediatric population with Kovanaze.

6   APPENDICES

6.1   APPENDIX A. PEDIATRIC LABELING CHANGES SUMMARY FOR KOVANAZE

Pediatric Labeling Date	Trade Name	Generic Name or Proper Name (*)	Indications Studied	Label Changes Summary	Therapeutic Category
06/29/2016	Kovanaze Nasal Spray	tetracaine HCl and oxymetazoline HCl	Regional anesthesia when performing a restorative procedure on teeth 4-13 and A-J in adults and children who weigh 40 kg or more	*Approved in adults and children who weigh 40 kg or more *Kovanaze has not been studied in pediatric patients under 3 years and is not advised for use in pediatric patients weighing less than 40 kg because efficacy has not been demonstrated in these patients *Information on adverse reactions in adults and pediatric patients, clinical trial, PK * New drug	Anesthetic, topical

Source: New Pediatric Labeling Information Database, FDA Office of Pediatric Therapeutics
https://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase;
accessed June 8, 2018.

6.2 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 post-marketing 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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