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

Date:	July 17, 2018
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Product Name:	OraVerse (phentolamine mesylate) injection
Pediatric Labeling Approval Date:	March 18, 2016
Application Type/Number:	NDA 022159
Applicant/Sponsor:	Septodont Holding
OSE RCM #:	2018-1176

EXECUTIVE SUMMARY

In accordance with the Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome for OraVerse (phentolamine mesylate) injection in pediatric patients.

OraVerse (phentolamine mesylate) injection was first approved on May 9, 2008 and is indicated for adult and pediatric patients ages 3 years and older for the reversal of soft-tissue anesthesia, (i.e., anesthesia of the lip and tongue), and the associated functional deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor.

There are currently no cases in the FDA Adverse Event Reporting System (FAERS) in pediatric patients for OraVerse. Therefore, there is no evidence from these data that there are pediatric safety concerns with OraVerse 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 Oraverse.

1 INTRODUCTION

OraVerse (phentolamine mesylate) injection is available as a dental cartridge, 0.4 mg/1.7 mL. It is indicated for adult and pediatric patients ages 3 years and older for reversal of soft-tissue anesthesia, (i.e., anesthesia of the lip and tongue), and the associated functional deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor.

1.1 PEDIATRIC REGULATORY HISTORY

The original OraVerse (NDA 022159, Septodont Holding) approval on May 9, 2008 included use in patients ≥6 years-old or weighing more than 15 kg (33 lbs). Per the Pediatric Research Equity Act (PREA), the Sponsor was required to conduct an OraVerse study in the lower pediatric age range between 2 and 6 years of age. FDA's review of the Sponsor's PREA study concluded that although there was a lack of suitable efficacy data for the 2-5 year-olds, the Sponsor did demonstrate safety and pharmacokinetic data that suggested no difference between 3-5 year-olds and older children and adults. By invoking FDA's prior experience with adult data, FDA determined that extrapolation of efficacy to pediatric patients was appropriate. FDA therefore granted the Sponsor an expansion to ≥3 years-old and weighing ≥15 kg (33 lbs) on **March 18, 2016**. The OraVerse Label Changes Summary from the Office of Pediatric Therapeutics' New Pediatric Labeling Information Database is in Appendix A.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

CONTRAINDICATIONS

OraVerse is contraindicated in patients with:
Hypersensitivity to the active substance or to any ingredients in the formulation.

WARNINGS AND PRECAUTIONS

Cardiovascular Events

Myocardial infarction, cerebrovascular spasm, and cerebrovascular occlusion have been reported to occur following the parenteral administration of phentolamine. These events usually occurred in association with marked hypotensive episodes producing shock-like states.
Tachycardia and cardiac arrhythmias may occur with the use of phentolamine or other alpha-adrenergic blocking agents. Although such effects are uncommon after administration of OraVerse, clinicians should be alert to the signs and symptoms of these events, particularly in patients with a prior history of cardiovascular disease.

ADVERSE REACTIONS

In clinical trials, the most common adverse reaction with OraVerse that was greater than the control group was injection site pain.

2 POSTMARKET ADVERSE EVENT REPORTS

2.1 METHODS

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 25, 2018
Time Period of Search	Entire database as of April 30, 2018
Search Type	Quick Query
Drug Name(s)	*Product Active Ingredient:* Phentolamine, Phentolamine hydrochloride, Phentolamine mesylate
	Product Name: Oraverse
	Product Verbatim Name: See Appendix C
Search Parameters	All ages, all outcomes, worldwide, NDA 022159

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 OraVerse (phentolamine mesylate) injection, 0.4 mg/1.7 mL

	All reports (US)	Serious† (US)	Death (US)
Adults(>17years)	10 (7)	7 (4)	1§ (1)
Pediatrics (0-≤17 years)	1 (0)	1 (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.
§This U.S. adult fatality (Case ID 9167349) is a female who did not receive OraVerse. She died after taking Fazaclo (clozapine orally disintegrating tablets). The FAERS record has the OraVerse NDA number, which is a miscode.
‡0 reports of pediatric deaths were identified among cases not reporting an age.

Our individual case review has determined that the single pediatric report is misclassified in Table 2. This is a foreign pediatric report (Case ID 9995544) of a female of unknown age who received OraVerse. The FAERS record shows her age to be 5-years-old,[a] however, this is a transcription error and the patient's correct age is unknown.

[a]This report was a 3500A (paper) submission. The character 'S' was typed into the Patient Age Box on the 3500A. The narrative reads: 'The case involves a female patient of unknown age.....' It appears that the FAERS data entry personnel mistook the 'S' as a '5' and further presumed 'years.'

3 DISCUSSION

There were no reports for OraVerse 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 OraVerse 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 OraVerse.

6 APPENDICES

6.1 APPENDIX A. PEDIATRIC LABELING CHANGES SUMMARY FOR OVAVERSE

Pediatric Labeling Date	Trade Name	Generic Name or Proper Name (*)	Indications Studied	Label Changes Summary	Therapeutic Category
03/18/2016	OraVerse Injection	phentolamine mesylate	Reversal of soft-tissue anesthesia	* Expanded indication down to pediatric patients 3 years and older; previously approved in 6 years and older. * Safety and efficacy have not been established in patients younger than 3 years. • Information on dosing and PK. * Postmarketing study	
05/09/2008	OraVerse Injection 0.4 mg (0.235 mg/mL)	phentolamine mesylate	Reversal of soft-tissue anesthesia, i.e., anesthesia of the lip and tongue, and the associated functional deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor	Use in children less than 6 years of age or weighing less than 15 kg (33 lbs) is not recommended Dosing information provided for children weighing 15 to 30 kg (66 lbs) Safety and efficacy were established in 2 clinical trials in children 12 to 17 years old, one trial in children ages 6 to 11 years, as well as adult studies Safety has been evaluated in pediatric patients under the age of 6 years but not efficacy Pharmacokinetics have been evaluated in children weighing 15 kg or more New indication	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 7, 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.

6.3 APPENDIX C. ORAVERSE VERBATIM DRUG NAMES FOR FAERS SEARCH

Table 3 OvaVerse Drug Verbatim Names For FAERS Search in Table 1
ORAVERSE
ORAVERSE 400 MICROGRAMS/1.7 ML SOLUTION FOR INJECTION
ORAVERSE INJECTION
ORAVERSE INJECTION (PHENTOLAMINE MESYLATE)
PHENTOLAMINE MESYLATE INJETION .4MG/ 1/7ML ORAVERSE

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

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