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:	November 4, 2024
Reviewers:	Omayma Kishk, PharmD, BCPPS, Safety Evaluator Division of Pharmacovigilance I (DPV-I) Ivone Kim, MD, Medical Officer DPV-I
Team Leader:	Carmen Cheng, PharmD DPV-I
Division Director:	Monica Muñoz, PharmD, PhD, BCPS DPV-I
Product Name:	Xyrem (sodium oxybate)
Pediatric Labeling Approval Date:	October 26, 2018
Application Type/Number:	NDA 021196
Applicant:	Jazz Pharmaceuticals, Inc.
TTT Record ID:	2023-7125

TABLE OF CONTENTS

Executive Summary 3
1 Introduction 4
1.1 Pediatric Regulatory History 4
1.2 Relevant Labeled Safety Information 4
2 Methods and Materials 5
2.1 FAERS Search Strategy 5
3 Results 6
3.1 FAERS 6
3.1.1 Total Number of FAERS Reports by Age 6
3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS 6
3.1.3 Summary of U.S. Fatal Pediatric Cases (N=0) 7
3.1.4 Summary of U.S. Serious Non-Fatal Pediatric Cases (N=1) 7
4 Discussion 8
5 Conclusion 8
6 References 9
7 Appendices 10
7.1 Appendix A. FDA Adverse Event Reporting System (FAERS) 10
7.2 Appendix B. FAERS Line Listing of the Pediatric Case Series (N=1) 11

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Xyrem (sodium oxybate) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with sodium oxybate in pediatric patients.

Xyrem (sodium oxybate) is a central nervous system depressant and was initially approved in the U.S. on July 17, 2002. Xyrem is currently indicated for for the treatment of cataplexy or excessive daytime sleepiness in patients 7 years of age and older with narcolepsy.

This pediatric postmarketing safety review was stimulated by pediatric labeling for Xyrem on October 26, 2018, for the treatment of cataplexy or excessive daytime sleepiness in pediatric patients 7 years of age and older with narcolepsy.

DPV reviewed all U.S. serious FAERS reports with sodium oxybate in pediatric patients less than 18 years of age from July 17, 2002 through December 13, 2023. Of the 449 reports reviewed, one case was included in our case series. The case described symptoms of angioedema; however, DPV determined there is insufficient information to support a signal at this time.

Overall, there were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with sodium oxybate in pediatric patients less than 18 years of age.

DPV will continue routine pharmacovigilance monitoring for sodium oxybate.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Xyrem (sodium oxybate) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with sodium oxybate in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Xyrem (sodium oxybate) is a central nervous system depressant and was initially approved in the U.S. on July 17, 2002. Xyrem is currently indicated for for the treatment of cataplexy or excessive daytime sleepiness in patients 7 years of age and older with narcolepsy.[1]

This pediatric postmarketing safety review was stimulated by pediatric labeling for Xyrem on October 26, 2018, for the treatment of cataplexy or excessive daytime sleepiness in pediatric patients 7 years of age and older with narcolepsy.[2]

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

1.2 RELEVANT LABELED SAFETY INFORMATION

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

WARNING: CENTRAL NERVOUS SYSTEM (CNS) DEPRESSION and ABUSE AND MISUSE.

See full prescribing information for complete boxed warning.

Central Nervous System Depression

- **Xyrem is a CNS depressant, and respiratory depression can occur with Xyrem use (5.1, 5.4)**

Abuse and Misuse

- **Xyrem is the sodium salt of gamma-hydroxybutyrate (GHB). Abuse or misuse of illicit GHB is associated with CNS adverse reactions, including seizure, respiratory depression, decreased consciousness, coma, and death (5.2, 9.2)**

Xyrem is available only through a restricted program called the XYWAV and XYREM REMS (5.3)

----------CONTRAINDICATIONS----------

•In combination with sedative hypnotics or alcohol (4)
•Succinic semialdehyde dehydrogenase deficiency (4)

----------WARNINGS AND PRECAUTIONS----------
•CNS depression: Use caution when considering the concurrent use of Xyrem with other CNS depressants (5.1).
•Caution patients against hazardous activities requiring complete mental alertness or motor coordination within the first 6 hours of dosing or after first initiating treatment until certain that Xyrem does not affect them adversely (5.1).
•Depression and suicidality: Monitor patients for emergent or increased depression and suicidality (5.5).
•Confusion/Anxiety: Monitor for impaired motor/cognitive function (5.6).
•Parasomnias: Evaluate episodes of sleepwalking (5.7).
•High sodium content in Xyrem: Monitor patients with heart failure, hypertension, or impaired renal function (5.8).

----------ADVERSE REACTIONS----------
Most common adverse reactions in adults (≥5% and at least twice the incidence with placebo) were nausea, dizziness, vomiting, somnolence, enuresis, and tremor (6.1).

Most common adverse reactions in pediatric patients (≥5%) were nausea, enuresis, vomiting, headache, weight decreased, decreased appetite, dizziness, and sleepwalking (6.1).

8.4 Pediatric Use

The safety and effectiveness of Xyrem in the treatment of cataplexy or excessive daytime sleepiness in pediatric patients (7 years of age and older) with narcolepsy have been established in a double-blind, placebo-controlled, randomized-withdrawal study *[see Adverse Reactions (6.1) and Clinical Studies (14.3)].*

In the pediatric clinical trial with Xyrem administration in patients with narcolepsy, serious adverse reactions of central sleep apnea and oxygen desaturation documented by polysomnography evaluation; depression; suicidal ideation; neuropsychiatric reactions including acute psychosis, confusion, and anxiety; and parasomnias, including sleepwalking, have been reported *[see Warnings and Precautions (5.4, 5.5, 5.6, 5.7) and Adverse Reactions (6.1)].*

Safety and effectiveness of Xyrem in pediatric patients below the age of 7 years have not been established.

Juvenile Animal Toxicity Data
In a study in which sodium oxybate (0, 100, 300, or 900 mg/kg/day) was orally administered to rats during the juvenile period of development (postnatal days 21 through 90), mortality was observed at the two highest doses tested. Deaths occurred during the first week of dosing and were associated with clinical signs (including decreased activity and respiratory rate) consistent with the pharmacological effects of the drug. Reduced body weight gain in males and females and delayed sexual maturation in males were observed at the highest dose tested. The no-effect dose for adverse effects in juvenile rats is associated with plasma exposures (AUC) less than that at the maximum recommended human dose (9 g/night).

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 1.

Table 1. FAERS Search Strategy*	
Date of search	December 14, 2023
Time period of search	July 17, 2002† - December 13, 2023
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product Active Ingredient: Sodium oxybate

Table 1. FAERS Search Strategy*	
MedDRA search terms (Version 26.1)	All Preferred Terms
* See Appendix A for a description of the FAERS database. † U.S. approval date Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports from July 17, 2002, through December 13, 2023, with sodium oxybate.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From July 17, 2002 through December 13, 2023, With Sodium Oxybate

	All Reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 18 years)	24,729 (23,655)	15,111 (14,328)	673 (561)
Pediatrics (0 - < 18 years)	1,159‡ (1,027)	512‡ (449)	14‡ (14)

* 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. The coded outcomes are report-level outcomes, i.e., they reflect any serious outcomes for any adverse events coded to a Preferred Term in the FAERS report. Therefore, a serious outcome may not apply to all adverse events in a FAERS report. A review of the FAERS report narrative is necessary to determine adverse event-level outcomes and any association to a suspect product.

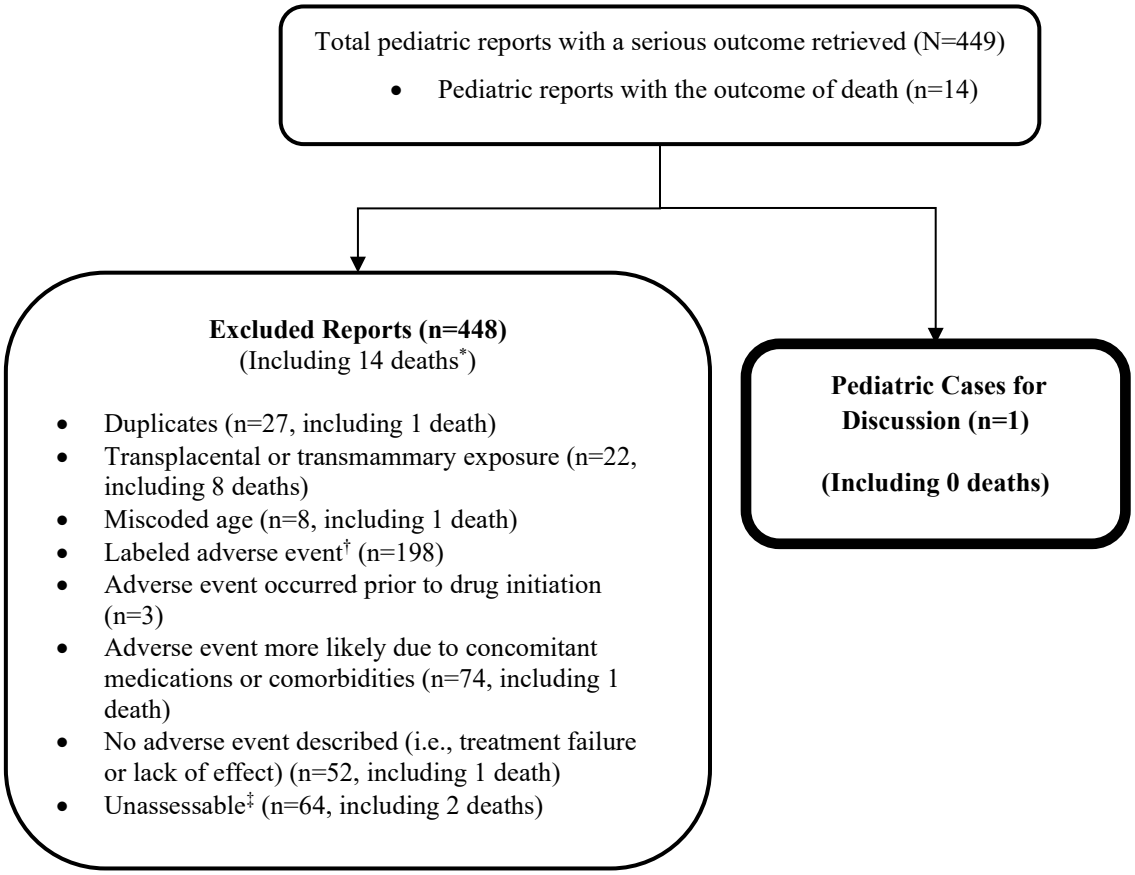
‡ See Figure 1. Six additional reports of U.S. pediatric deaths were identified among reports not reporting an age. These reports are reflected in the counts of pediatric reports.

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

Our FAERS search retrieved 449 U.S. serious pediatric reports from July 17, 2002, through December 13, 2023. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded 448 reports from the case series for the reasons listed in Figure 1. Figure 1 presents the selection of cases for the pediatric case series.

Appendix B contains a line listing of the one pediatric case in the case series.

Figure 1. Selection of U.S. Serious Pediatric Cases With Sodium Oxybate



* Fourteen excluded U.S. FAERS reports described fatal outcomes. After accounting for duplicate reporting, DPV identified 13 unique cases describing a fatal outcome. None of the deaths were determined to be attributed to sodium oxybate. Of these, eight excluded death cases described patients who had transplacental or transmammary exposure to sodium oxybate. For six of the eight cases, the cause of death was prematurity (n=2), sudden infant death syndrome rather than drug (n=2), "rare brain disorder" with a short life expectancy (n=1), or fetal arrthymia and congestive heart failure (n=1); the remaining two cases did not provide sufficient clinical information to determine the cause of death. Of the remaining five death cases, one case involved a 33-year-old adult (miscoded with pediatric age) who died due to aspiration pneumonia. One case described a patient who died from complications from her primary medical condition of seizures. One case did not describe an adverse drug event (i.e., patient was a victim of homicide). Two death cases lacked sufficient clinical information to perform a causality assessment with sodium oxybate.

† Labeled adverse event does not represent increased severity.

‡ Unassessable: The report cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome), the information is contradictory, or information provided in the report cannot be supplemented or verified.

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=1)

We identified one U.S. pediatric FAERS case with sodium oxybate reporting a non-fatal serious outcome.

FAERS #10246028 involves a 17-year-old male on sodium oxybate 3.75 grams twice daily for the treatment of narcolepsy with cataplexy. On his second night of sodium oxybate, he developed hives all over his body, lip swelling, facial swelling, difficulty breathing, and worsening cataplexy. The patient discontinued sodium oxybate therapy. The outcome for the reported adverse events is not reported.

Reviewer's comment: The case describes symptoms of angioedema. The positive temporal relationship between angioedema symptoms and sodium oxybate supports a possible causal association. However this case does not provide any additional clinical details to confirm sodium oxybate as the culprit medication such as use of concomitant medications or if the patient recovered after discontinuation of sodium oxybate. Of note, sodium oxybate is labeled for "hypersensitivity" in Section 6.2 Postmarketing Experience subsection of the ADVERSE REACTIONS section of the labeling. DPV finds there is insufficient information to support a signal at this time.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with sodium oxybate in pediatric patients less than 18 years of age from July 17, 2002, through December 13, 2023. Of the 449 reports reviewed, one case was included in our case series. The case described symptoms of angioedema; however, DPV determined there is insufficient information to support a signal at this time.

Overall, there were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with sodium oxybate in pediatric patients less than 18 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Xyrem® (sodium oxybate) oral solution [Prescribing Information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. ; April 2023.
2. Mani R. Medical Officer Review for NDA 21196 (S-030), Xyrem® (sodium oxybate). October 2018. https://www.fda.gov/media/166510/download?attachment

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.

7.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=1)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control # or Central Triage Unit #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome*
1	17-JUN-2014	10246028	1	2014-US-007150	15-DAY	17	Male	USA	OT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those that are blank were not marked as serious (per the previous definition) by the reporter and are coded as non-serious. A case can have more than one serious outcome. The coded outcomes are report-level outcomes, i.e., they reflect any serious outcomes for any adverse events coded to a Preferred Term in the FAERS report. Therefore, a serious outcome may not apply to all adverse events in a FAERS report. A review of the FAERS report narrative is necessary to determine adverse event-level outcomes and any association to a suspect product.
Abbreviations: OT=other medically significant