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August 30, 2022

Sandra Retzky, D.O., J.D., MPH
Director, Office of Orphan Products Development
Office of Clinical Policy and Programs
Food and Drug Administration
WO-32, Room 5295
10903 New Hampshire Ave.
Silver Spring, MD 20993

RE: Orphan Drug Considerations for LUMRYZ™ (sodium oxybate) for Extended-Release Oral Suspension – DRU 2016-5302

Dear Dr. Retzky,

Avadel CNS Pharmaceuticals, LLC ("Avadel") submits this correspondence to the Food and Drug Administration ("FDA") Office of Orphan Products Development ("OOPD") regarding orphan drug considerations for its proprietary product candidate, LUMRYZ (sodium oxybate) for extended release oral suspension (formerly FT218), which is the subject of a pending new drug application ("NDA") for treatment of cataplexy or excessive daytime sleepiness ("EDS") in adults with narcolepsy (NDA 214755). Avadel received orphan drug designation for LUMRYZ for treatment of narcolepsy on January 8, 2018 based on a plausible hypothesis of clinical superiority over XYREM (sodium oxybate) oral solution (NDA 021196) (DRU 2016-5302).

FDA approved XYREM for treatment of cataplexy and EDS in narcolepsy in 2002 and 2005, respectively. On July 21, 2020, FDA approved a mixed salts version of sodium oxybate, XYWAV (calcium, magnesium, potassium, and sodium oxybates) oral solution (NDA 212690), and on June 24, 2021, FDA granted XYWAV orphan drug exclusivity over XYREM. Both XYREM and XYWAV are marketed by Jazz Pharmaceuticals, Inc. ("Jazz"). Both drug products are immediate release ("IR") formulations of sodium oxybate that require twice-nightly dosing, once at bedtime and again 2.5 to 4 hours later.

Avadel submitted its NDA for LUMRYZ on December 15, 2020. LUMRYZ is a proprietary, extended-release ("ER") formulation of sodium oxybate that is administered once-nightly via a single dose at bedtime. Avadel's original NDA submission for LUMRYZ contained a demonstration of clinical superiority over XYREM, and on July 15, 2021, Avadel submitted a supplemental demonstration of clinical superiority over both XYREM and XYWAV. On July 18, 2022, FDA granted tentative approval to the LUMRYZ NDA due to ongoing patent litigation with Jazz.

This correspondence is intended to share the results of new research with OOPD regarding a serious safety risk associated with both IR oxybate formulations to further support the clinical superiority of LUMRYZ over XYREM and XYWAV.

Inappropriate Schedule of Dosing Administration and Accidental Overdose with Twice-Nightly IR Oxybate Products

Pursuant to the approved Prescribing Information ("PI") for XYREM and XYWAV, the total nightly dosage of each respective drug is divided into two doses, and patients are instructed to prepare both doses prior to bedtime.[1] Prior to ingestion, patients are instructed to withdraw the appropriate dose of the oral solution via syringe and dilute it with water; patients are then instructed to take the first nightly dose at bedtime (at least 2 hours after eating) and take the second nightly dose at least 2.5 hours but no more than 4 hours after the first dose. The PI states that patients should take both doses while in bed, lie down immediately after dosing, and remain in bed following ingestion of each dose. The PI also states that patients may need to set an alarm to awaken for the second dose, and if the second dose is missed, that dose should be skipped and XYREM or XYWAV should not be taken again until the next night. The PI warns that two doses should never be taken at one time.

In the pivotal trial for XYWAV (n=201), a serious adverse drug reaction was reported after a patient inadvertently took the second dose of XYWAV shortly after the first dose.[2] Both doses were 4.5 g, totaling the maximum approved total nightly dosage of 9 g. The participant experienced confusion and hallucinations and was hospitalized, with discharge after symptom resolution. Similarly, in a post-market study in Europe, an 18-year-old female also experienced accidental overdose due to an inappropriate schedule of drug administration, where the patient took the second dose of XYREM immediately after the first.[3] The patient was hospitalized overnight.

Because of the inherent potential for accidental dosing administration errors of this type with an IR oxybate formulation that must be administered twice-nightly, once in the middle of the night, Avadel undertook to examine FDA's Adverse Event Reporting System ("FAERS") database to better assess this safety risk and further underscore the benefit of a once-nightly ER oxybate product.

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[1] XYWAV is also approved for treatment of idiopathic hypersomnia via once-nightly dosing of a maximum dosage of 6 g; however, the labeling instructions for dosing and administration of XYREM and XYWAV for the treatment of narcolepsy are the same. *See* XYREM PI (Rev. Mar. 2022), http://pp.jazzpharma.com/pi/xyrem.en.USPI.pdf; XYWAV PI (Rev. Mar. 2022), https://www.xywav.com/pdf/xywav.en.USPI.pdf.

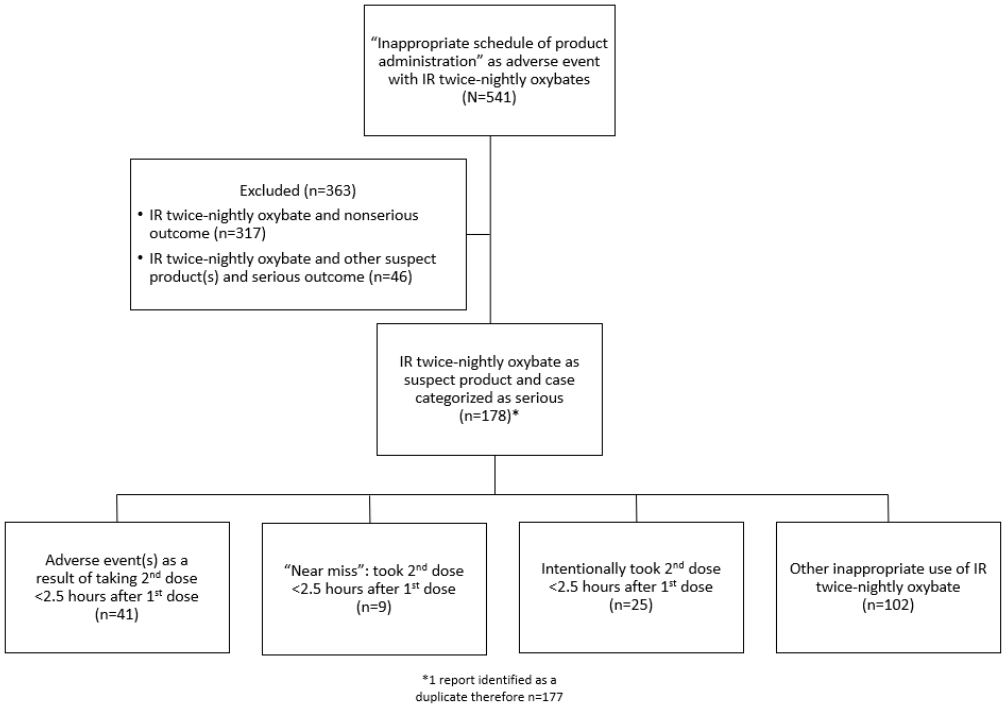
[2] Bogan, et al., *Efficacy and Safety of Calcium, Magnesium, Potassium, and Sodium Oxybates (Lower-Sodium Oxybate [LXB]; JZP-258) in a Placebo-Controlled, Double-Blind, Randomized Withdrawal Study in Adults with Narcolepsy with Cataplexy*, Sleep (2021): 44(3), 1-13, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7953213/pdf/zsaa206.pdf.

[3] Mayer, et al., *Long-Term Compliance, Safety, and Tolerability of Sodium Oxybate Treatment in Patients with Narcolepsy Type 1: A Postauthorization, Noninterventional Surveillance Study*, Sleep (2018): 41(9), 1-8, https://academic.oup.com/sleep/article-pdf/41/9/zsy128/25714959/zsy128.pdf.

The FAERS Public Dashboard was searched via the "Search by Product" feature using product names "Xyrem," "Xywav," "sodium oxybate," and "calcium oxybate\magnesium oxybate\potassium oxybate\sodium oxybate." The list of reported reactions was reviewed to identify the term most likely to capture incidents of patients taking an IR oxybate not according to the instructions in the PI. The Medical Dictionary for Regulatory Activities ("MedDRA") preferred term "inappropriate schedule of product administration" was used to identify reports in which the second dose may not have been taken as required. The search criteria were further refined to only include reports in which the IR oxybate product was the "Suspect Product" and for which the case outcome was classified as "serious," (i.e., death, life-threatening, hospitalization, disability or permanent damage, congenital anomaly/birth defect, or other serious or important medical event that may jeopardize the patient). The identified FAERS reports were then requested from FDA under the Freedom of Information Act ("FOIA"). All FAERS reports were analyzed by two separate reviewers to adjudicate relevant reports for inclusion in the analysis, i.e., those in which the patient took the second dose of IR oxybate less than 2.5 hours after the first dose and experienced an adverse event.

For the FAERS data available through March 31, 2022, there were a total of 541 reports that included the preferred term of "inappropriate schedule of product administration" as a reaction with either IR oxybate product. Of the 541 reports identified, there were 178 reports in which IR oxybate was the suspect product and the patient had a serious outcome. During the timeframe from July 2021 through July 2022, the 178 reports meeting the search criteria were requested under FOIA and reviewed. Upon review, one report was identified as a duplicate and removed from the analysis. Forty-one reports, all classified as serious, described patients accidentally taking their second dose of IR oxybate less than 2.5 hours after the first dose and experiencing one or more adverse events as a result (**Figure 1**). All 41 reports of interest were submitted to FDA by the manufacturer, Jazz, between August 2011 and November 2020.

Figure 1: Flow Chart of FAERS Reports Identified and Included in Analysis



A brief description of the 41 reports is attached (**Appendix 1**). Twenty-six (63%) reports involved female patients, and the age of the affected patients ranged from 7-65 years old with an average of 42 years. Nine (22%) reports described incidents involving emergency medical services or emergency department visits, and eleven (27%) reports described incidents resulting in hospitalization. Ten (24%) reports were initially reported by the American Association of Poison Control Centers ("AAPCC"). One report involved a patient who had a tendency to take her second dose 30 minutes to 1.5 hours after the first dose; upon her death, XYREM was noted as possibly contributing.

Timing of dosing errors varied: eight (20%) took their two doses at the same or almost the exact same time; eight (20%) took their second dose less than 1 hour after the first dose; and twenty-five (61%) took the second dose between 1 and 2.5 hours after the first dose. Harm to patients was described more frequently when patient took their second dose 1 hour or less after their first dose. Adverse events reported with accidentally taking the second dose too early included central nervous system ("CNS") depression, bradycardia, respiratory depression, dizziness, seizure, confusion, delirium, difficulty awakening, drowsiness, falls, nausea, vomiting, and enuresis.

Some narratives described patients being fearful of continuing IR oxybate, with either confirmed discontinuation or consideration of discontinuation, because they feared that the error would occur again. In one report, the patient became fearful after realizing she had taken her dose too soon and forced herself to vomit and remain awake as long as she could to ensure she continued breathing.

Contributing factors to patients consuming the second dose less than 2.5 hours after the first dose included distraction, forgot, and/or restarted routine; sleepwalking; did not check or readjust alarm clock to make sure enough time passed; misunderstood frequency prescribed or misread directions; and not recognizing that two doses were added to the same container.

For reports not considered relevant for inclusion in this study, nine represent near misses where patients accidentally took the second dose less than 2.5 hours after the first dose but had no associated adverse event(s). Additionally, there were twenty-five reports in which the patient intentionally took the second dose early. The remaining one hundred and two reports involved other inappropriate use of IR oxybate, such as taking the second dose more than 4 hours after the first dose or not taking the medication daily as prescribed (**Figure 1**).

In addition to Avadel's FAERS database analysis, Avadel provided sixty-five of the collected reports to the (b) (4), for further analysis of inappropriate product administration with IR oxybate. The 65 provided reports included serious cases associated with both accidental and intentional dosing of IR oxybate less than 2.5 hours apart that resulted in adverse events, as well as those that did not cause adverse events and reports of dosing more than 4 hours after the first dose. Note that the number of reports differed between (b) (4) and Avadel because Avadel's analysis included only those cases associated with adverse events in which the patient accidentally took the second dose less than 2.5 hours after the first dose. Also, during the time that (b) (4) performed its analysis, Avadel continued requesting and receiving additional FAERS reports. The resulting (b) (4) report is attached (**Appendix 2**). The report confirmed that dosing frequency errors may occur in patients who are prescribed IR oxybates with greater risk of harm present when patients take their second dose too early, particularly when the second dose is taken 1 hour or less after the first dose.

* * * *

Avadel's FAERS analysis demonstrates that serious risks can and do occur with improper administration of the second, middle-of-the night dose of XYREM and XYWAV. This is particularly concerning in the intended narcolepsy patient population since narcolepsy patients may experience automatic behaviors and/or brain fog[4], which could make them more likely to accidentally take their second dose prior to the prescribed 2.5-4 hour timeframe after the first dose. The frequency of improper product administration resulting in serious adverse events indicates a potential significant safety risk associated with both twice-nightly IR oxybate formulations.

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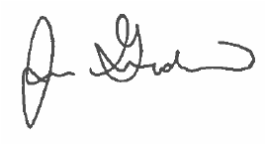
[4] US Food and Drug Administration, *The Voice of the Patient. A series of reports from the U.S. Food and Drug Administration's (FDA's) Patient-Focused Drug Development Initiative. Narcolepsy,* Summary Report (2014), Available at: https://www.fda.gov/media/88736/download

By providing a once-nightly dosing option, Avadel's LUMRYZ stands to eliminate the need for a second middle-of-the-night dose, greatly reducing the risk of dosing errors, accidental overdose, and associated patient harm. This significant improvement in patient safety further supports Avadel's demonstration of clinical superiority of LUMRYZ over XYREM and XYWAV for purposes of orphan drug exclusivity upon approval.

Avadel thanks OOPD for its consideration of the information and data discussed in this correspondence. Please do not hesitate to contact me with any questions at (314) 750-2751 or jgudeman@avadel.com.

Sincerely,



Jennifer Gudeman, PharmD
Vice President, Clinical & Medical Affairs
Avadel CNS Pharmaceuticals, LLC

Attachments

Appendix 1

Line Listing of FAERS Reports of Interest

FAERS Report Number	Report Priority for FDA	Initial FDA Receipt Date	Patient Sex	Patient Age (years)	Dosing Error
8086716	Expedited	02-AUG-2011	Male	63	Took by error 2nd dose 10 minutes after 1st dose
8148479	Expedited	07-SEP-2011	Female	63	Inadvertently took 2nd dose before 2.5 hours after 1st dose
9407996	Expedited	22-APR-2013	Female	43	Took 2nd dose 1.5 hours early
10172732	Expedited	13-MAY-2014	Female	53	Took 1st dose, began nightly routine and accidentally took 2nd dose after just having taken the 1st
10229851	Expedited	09-JUN-2014	Male	23	Took 2nd dose 1.5 hours after 1st dose
10645638	Expedited	09-DEC-2014	Male	7	Patient's mother administered 2 doses within a too short period between doses (2 hours)
10836059*	Expedited	19-FEB-2015	Male	52	Took 1st dose and 1 hour later without thinking accidentally took 2nd dose
12442374	Expedited	07-JUN-2016	Female	34	Ingested 2 doses close to the same time; patient's son did not know that she had taken her 1st dose and accidentally gave her 2nd dose
12497430	Expedited	24-JUN-2016	Female	Not provided	Took 2nd dose immediately after 1st dose because forgot had taken 1st dose
12581349	Expedited	21-JUL-2016	Female	63	Inadvertently took 2nd dose when awoke and thought it was time to take but it was too early
12620152	Expedited	03-AUG-2016	Male	Unknown	Took doses 2 hours apart
13052535	Expedited	21-DEC-2016	Female	49	Took 2nd dose too early while sleepwalking

FAERS Report Number	Report Priority for FDA	Initial FDA Receipt Date	Patient Sex	Patient Age (years)	Dosing Error
13156675	Non-Expedited	26-JAN-2017	Female	18	Took doses too close together
13441020	Expedited	13-APR-2017	Female	38	Accidentally took 2nd dose 1 hour after 1st dose
13500013	Expedited	01-MAY-2017	Female	53	Took 1st dose and accidentally took 2nd dose right after 1st without thinking
14074197	Expedited	11-OCT-2017	Female	54	Took 2nd dose 2 hours after 1st dose; didn't realize had taken doses too close together
14080329	Expedited	12-OCT-2017	Female	61	Accidentally took 2nd dose approximately 1 hour after taking 1st dose
14442031	Expedited	25-JAN-2018	Female	62	Woke up in the middle of the night and did not pay attention to alarm clock and overlapped doses; was about 1.5 hours after 1st dose
14650306	Expedited	16-MAR-2018	Male	17	Patient was given 2nd dose 2 hours after 1st dose
14800123	Expedited	24-APR-2018	Male	65	Accidentally took a double dose; tired when preparing doses and ran out of medication in current bottle, got new bottle to finish drawing up doses and got distracted and put both doses into one dosing container
14844046	Non-Expedited	03-MAY-2018	Male	34	Took 2nd dose about 2 hours after 1st dose instead of 4 hours because thought it was time to take 2nd dose
14854175	Expedited	07-MAY-2018	Male	65	Accidentally took 2nd dose 30 minutes after 1st dose
14914500	Expedited	18-MAY-2018	Male	15	Accidentally took doses about 30 minutes apart
14914593	Non-Expedited	18-MAY-2018	Female	48	Inadvertently took 2 doses too close together

FAERS Report Number	Report Priority for FDA	Initial FDA Receipt Date	Patient Sex	Patient Age (years)	Dosing Error
14923710	Expedited	22-MAY-2018	Male	44	Unintentionally took 2nd dose 30 minutes after 1st dose
14927962	Expedited	23-MAY-2018	Female	57	Inadvertently took 2 doses, one shortly after the other; took dose, went to the bathroom and when came back, forgot had already taken 1st dose and took 2nd dose
15588213	Non-Expedited	05-NOV-2018	Female	40	Accidentally took double dose
15608982	Expedited	12-NOV-2018	Female	41	Woke up 1 hour and 45 minutes after taking 1st dose and took 2nd dose at that time
15992034	Expedited	21-FEB-2019	Female	55	Took 1st dose and then got distracted; went back to bed, forgot already took 1st dose and took 2nd dose about 15 minutes apart
16171676	Non-Expedited	08-APR-2019	Male	33	Accidentally took 2nd dose approximately 1 hour after taking 1st dose
16882499	Non-Expedited	03-OCT-2019	Female	46	Inadvertently took a double dose 1 hour apart
17000238	Expedited	06-NOV-2019	Female	26	Accidentally took 2 doses together
17422250	Expedited	14-FEB-2020	Male	30	Unintentionally took both doses at the same time
17503945	Expedited	05-MAR-2020	Male	14	Given doses too close together by mistake by parents
17547622	Expedited	16-MAR-2020	Female	33	Unintentionally took doses too close together
17758591	Expedited	07-MAY-2020	Female	26	Took 1st dose, forgot about it, and took 2nd dose approximately 30 minutes after 1st dose

FAERS Report Number	Report Priority for FDA	Initial FDA Receipt Date	Patient Sex	Patient Age (years)	Dosing Error
17965625	Non-Expedited	30-JUN-2020	Female	23	Doses unintentionally taken too close together
18108233	Expedited	03-AUG-2020	Male	60	Took 2nd dose 1.5 hours after 1st dose because of misreading the clock
18377576	Expedited	13-OCT-2020	Female	50	Tendency to take 2nd dose before 2.5 hours
18491354	Expedited	11-NOV-2020	Female	24	Unintentionally took 2nd dose 2 hours later
18491355	Expedited	11-NOV-2020	Female	57	Unintentionally took 2nd dose 30 minutes after 1st dose

*FAERS Report Number 10996114 identified to be a duplicate of 10836059.

Appendix 2

(b) (4) **Report**

Error Analysis

Evaluation of Immediate-Release Oxybate Wrong Frequency Errors

Prepared for

Avadel CNS Pharmaceuticals, LLC

Prepared by

(b) (4)

August 8, 2022

(b) (4)

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(b) (4)

Introduction and Background

Introduction

On behalf of Avadel CNS Pharmaceuticals, LLC (Avadel) (b) (4) (b) (4) performed an analysis of wrong frequency errors associated with the use of immediate-release oxybate products, which are indicated for the treatment of patients with narcolepsy. Sodium oxybate and other oxybate salts are administered by patients or caregivers in two nightly doses, separated by 2.5 to 4 hours. Using data collected from the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS), this analysis intended to identify immediate-release oxybate administration errors in which the second dose is not administered within the recommended timeframe (2.5 to 4 hours). Additionally, this evaluation aimed to quantify and categorize these events, as well as any resulting patient harm and contributing factors that may be associated with the inappropriate dosing schedule.

Background

Narcolepsy is a sleep disorder that affects the brain's ability to control sleep-wake cycles and is characterized by symptoms such as excessive daytime sleepiness, sleep paralysis, cataplexy (sudden loss of muscle tone), and sleep-related hallucinations. The condition is mainly categorized into two types, type 1 (narcolepsy with cataplexy) and type 2 (narcolepsy without cataplexy).[1-2] While narcolepsy is recognized as a disease state that is often underdiagnosed, in the US, it has been estimated that 44.3 per 100,000 persons have narcolepsy.[3] Narcolepsy can have a significant effect on an individual's day-to-day activities, particularly if left undiagnosed or untreated. While narcolepsy is a lifelong neurological disorder, certain therapies, such as sodium oxybate and other oxybate salts, can be used to help control patient symptoms.[1-2]

Sodium oxybate (Xyrem) is currently approved by the US Food and Drug Administration (FDA) for the treatment of cataplexy or excessive daytime sleepiness in patients with narcolepsy who are 7 years of age and older. Oxybate as calcium, magnesium, potassium, and sodium salts is also approved for use in the US under the proprietary name Xywav for the same indication, as well as for the treatment of idiopathic hypersomnia in adults. Xyrem and Xywav are both supplied as a 500 mg/mL oral solution in a 180 mL bottle, which needs to be diluted before use.[4-7]

The initial starting dose of Xyrem or Xywav for narcolepsy in adults is 2.25 g at bedtime, followed by 2.25 g administered 2.5 to 4 hours later. The total nightly dose, divided in two doses, may be increased by 1.5 g at weekly intervals to an effective dosage range of 6 to 9 g per night. Prior to bedtime, patients should prepare both of their Xyrem or Xywav doses, and prior to ingestion, each dose should be diluted in approximately 60 mL of water in containers provided by the pharmacy. Patients are instructed to take both doses while in bed and that they may need to set an alarm to awaken for the second dose.[4-7]

As central nervous system (CNS) depressants, sodium oxybate and other oxybate salts are contraindicated if used concomitantly with alcohol or sedative-hypnotic agents that may enhance the CNS depressant effects, such as benzodiazepines. Xyrem should be used with caution in patients with cardiovascular disease and renal impairment due to its high sodium content, and both Xyrem and Xywav should be used with caution in patients with hepatic impairment. Adverse effects associated with the use of Xyrem or Xywav include CNS effects (e.g., CNS depression, headache, confusion, drowsiness, dizziness, parasomnias, anxiety, depression, suicidal ideation), respiratory depression, gastrointestinal effects (e.g., nausea, vomiting, decreased appetite), urinary incontinence, and weight loss. Due to the potential CNS effects, patients should not engage in activities that require mental alertness or motor coordination (e.g., operating machinery, driving) for at least 6 hours after taking a dose.[4-7]

Both Xyrem and Xywav are only available through a restricted program, the Xywav and Xyrem Risk Evaluation and Mitigation Strategy (REMS), which has prescriber and pharmacy components for assuring safe use, limits distribution only to a participating central pharmacy, and requires patients to be enrolled in the REMS program.[4-7]

References:

1. Sleep Foundation. Narcolepsy. Updated March 18, 2022. Available at: https://www.sleepfoundation.org/narcolepsy. Accessed July 20, 2022.
2. NINDS. Narcolepsy Fact Sheet. Available at: https://www.ninds.nih.gov/narcolepsy-fact-sheet. Accessed July 20, 2022.
3. Acquavella J, Mehra R, Bron M, Suomi JM, Hess GP. Prevalence of narcolepsy and other sleep disorders and frequency of diagnostic tests from 2013–2016 in insured patients actively seeking care. *J Clin Sleep Med*. 2020;16(8):1255-63.
4. Xyrem [package insert]. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; 2018.
5. Xywav [package insert]. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; 2020.
6. Xyrem. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Available at: http://online.lexi.com. Accessed July 18, 2022.
7. Xywav. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Available at: http://online.lexi.com. Accessed July 18, 2022.

Methods

To identify any potential wrong frequency errors associated with the use of Xyrem or Xywav, Avadel performed a search of the FAERS Public Dashboard using the product terms "Xyrem," "Xywav," "Sodium Oxybate," and "Calcium Oxybate/Magnesium Oxybate/Potassium Oxybate/Sodium Oxybate." The search was then refined by reaction, using the MedDRA preferred term of "Inappropriate schedule of product administration." Avadel further narrowed the search to only those reports in which "Xyrem," "Xywav," "Sodium Oxybate," or "Calcium Oxybate/Magnesium Oxybate/Potassium Oxybate/Sodium Oxybate" was listed as the suspect drug and the case report was categorized as "serious." These search results represented FAERS data received through December 31, 2021. Avadel then submitted a Freedom of Information Action (FOIA) request to the FDA to obtain the identified FAERS reports. Once received, Avadel reviewed the reports and provided a subset to MSB for analysis as a part of this evaluation.

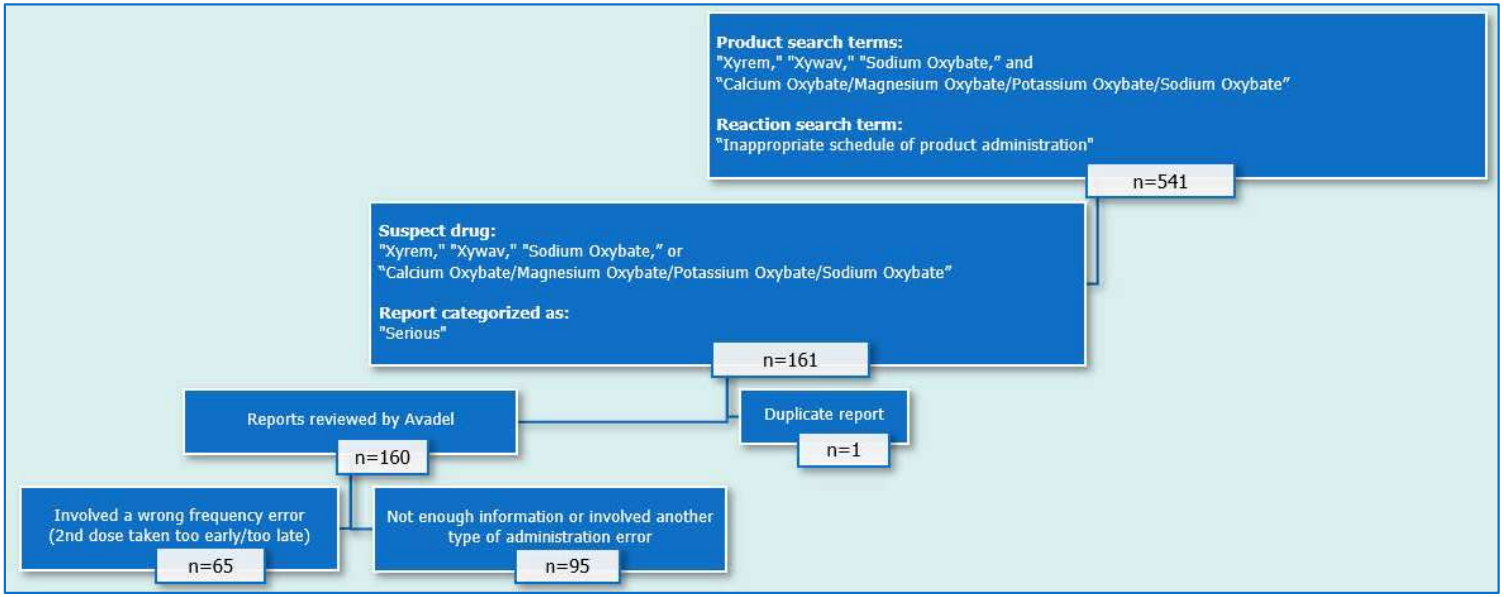
An MSB pharmacist reviewed the subset of FAERS reports provided by Avadel for wrong frequency errors involving Xyrem or Xywav. These events were categorized and described by type (second dose administered less than 2.5 hours after the first dose, second

dose administered more than 4 hours after the first dose, and second dose not administered), resulting patient outcome or harm, and any contributing factors. Other types of administration errors, such as taking more than two doses nightly or wrong dilution errors, were excluded from analysis.

Results

The search performed by Avadel of the FAERS Public Dashboard using the product terms "Xyrem," "Xywav," "Sodium Oxybate," and "Calcium Oxybate/Magnesium Oxybate/Potassium Oxybate/Sodium Oxybate," and the reaction term "Inappropriate schedule of product administration" returned 541 reports, as of December 31, 2021 (see **Figure 1**). The number of these reports identified by Avadel in which "Xyrem," "Xywav," "Sodium Oxybate," or "Calcium Oxybate/Magnesium Oxybate/Potassium Oxybate/Sodium Oxybate" was listed as the suspect drug and the case report was categorized as "serious" was 161. Upon review by Avadel, one of these reports was determined to be a duplicate, leaving 160 total unique reports. Avadel further reviewed the remaining 160 reports for events in which the patient inappropriately administered the second dose of Xyrem or Xywav outside of the recommended timeframe, identifying 65 reports to be included for this evaluation. The other 95 reports were deemed by Avadel as not containing enough information to determine if the second dose had been inappropriately administered prior to or after the recommended window of 2.5 to 4 hours or involved another type of wrong administration error, such as taking three nightly doses.

Figure 1.



(b) (4)

Patient and Case Report Characteristics

Based on the 65 FAERS case reports included for analysis, a little over half (54%) involved female patients and 46% involved male patients (see **Table 1**). The age of six of the patients was unknown, with the age of the remaining 59 patients ranging from 7 to 77 years of age. Most (40%) were between 40 and 59 years old, with 12% less than 20 years of age, 20% between 20 and 39 years of age, and 18% 60 years of age or older.

Most (95%) of the case reports involved the administration of Xyrem as the suspect drug, with only three reports involving Xywav. Narcolepsy or narcolepsy with cataplexy was listed as the known indication for Xyrem or Xywav use in most (82%) patients. Of note, one patient was later determined to be misdiagnosed with narcolepsy, and treatment with Xyrem was stopped. The indication for the remaining 12 patients (18%) was either unknown (n=7) or was listed as excessive daytime sleepiness (n=1), insomnia (n=1), insomnia and fibromyalgia (n=2), or sleep disorder (n=1).

While in many cases (n=19, 29%), the dose prescribed to the patient at the time of the wrong frequency error was unknown or unclear based on the provided information, in the reports in which the dose was described or could be identified, the nightly dose ranged from 1 g BID in a pediatric patient to 5.5 g BID in an adult patient (note: 5.5 g BID exceeds the recommended nightly dosage). Most patients (31%) were prescribed 4 g or 4.5 g BID nightly. In two cases, while the patient was prescribed 4.5 g BID, the event description indicated that the patient took more doses than prescribed. A few patients (9%) were noted as taking a different dose for their first dose compared to their second dose, for example, one patient took 3.75 g for their first dose and 4 g for their second dose.

Table 1. Patient Characteristics

	n (%)
Sex	
Female	35 (54%)
Male	30 (46%)
Age (in years)	
Unknown	6 (9%)
19 or younger	8 (12%)
20 to 39	13 (20%)
40 to 59	26 (40%)
60 or older	12 (18%)
Medication	
Xyrem	62 (95%)
Xywav	3 (5%)
Indication	
Unknown	7 (11%)
Narcolepsy or Narcolepsy with cataplexy	53 (82%)
Other*	5 (7%)
Prescribed nightly dose (at time of error)	
Unknown or unclear	19 (29%)
1 g BID	1 (1.5%)
2 to 2.5 g BID	9 (14%)
3 to 3.75 g BID	9 (14%)
4 to 4.5 g BID	20 (31%)
5.5 g BID	1 (1.5%)
Different 1st dose compared to 2nd dose	6 (9%)

*excessive daytime sleepiness (n=1), insomnia (n=1), insomnia and fibromyalgia (n=2), sleep disorder (n=1)

More than half (n=39, 60%) of the reports were solicited REMS reports, with 34% described as spontaneous reports from consumers, caregivers, and healthcare professionals, including 14% that were reported by the American Association of Poison Control Centers (AAPCC). While the event year for the identified wrong frequency error(s) may have been unknown or unclear in about one-third (35%) of the reports, most (n=35, 54%) occurred within the past five years (between 2016 and 2021).

(b) (4)

Error Types

In reviewing the 65 case reports, while all contained at least one wrong frequency error, many of the reports also contained other reactions or adverse event information that did not appear to have an association with the error. Thus, while all reports were categorized as "serious" in the FAERS database, the error itself may not have been associated with a serious event. Most (91%) of the 65 cases that were reviewed described an event in which the patient took their second dose of Xyrem or Xywav too early (before the recommended 2.5-hour window) on one or more occasions. Six (9%) of the reports described an event in which the patient took their second dose too late (more than 4 hours after the first dose). A few of the reports described more than one frequency error type, with seven reports (11%) also mentioning instances in which the second dose was not administered at all, in addition to instances in which they either took it too early or too late.

Second dose taken too early (less than 2.5 hours after the first dose)

Fifty-nine (91%) of the 65 case reports involved patients taking their second dose of Xyrem or Xywav before the minimum 2.5 hours. In eight of these 59 cases (14%), the exact timing of when the second dose was administered was unknown, other than that it had been administered too soon. Of those in which the number of hours was noted, about half (n=24, 47%) were given in 1 hour or less from the first dose, including 11 instances in which the patient took their two doses at the same or almost the exact same time. The other half (n=27, 53%) administered their second dose between 1 and 2.5 hours after the first dose.

Of the 24 reports in which the patient took their second Xyrem or Xywav dose 1 hour or less after their first dose, the majority (n=19, 79%) reported an adverse event, including 13 that indicated the patient required an emergency department (ED) visit or hospitalization for monitoring and/or intervention. Of the 27 reports in which the patient took their second dose more than 1 hour but less than 2.5 hours after their first dose, only 7 (26%) described an adverse event that appeared to be associated with the error, with 3 reporting that the patient required an ED visit or hospital admission.

An adverse event was described as being associated with 32 (54%) of the 59 "too early" administration errors, including at least 19 serious reports in which the patient went to the ED or was hospitalized (32%). In forty-one percent of the cases (n=24), an adverse event was not noted as occurring as a result of the frequency error. For three cases, it was not clear if the reported adverse event was related to Xyrem or Xywav use, or more specifically, to the patient taking their second dose too early. For example, in one report, the caregiver found the patient collapsed in bed and started cardiopulmonary resuscitation (CPR), but the patient later expired. The patient had a tendency to take her doses before the 2.5 hours, but it was unclear if this resulted in the patient's fatal outcome. Also, at least three of the reports describing a serious adverse event, contained confounding issues, such as the coadministration of other CNS depressant agents, such as Lunesta (eszopiclone), Xanax (alprazolam), or alcohol. At least another report described a patient with a serious adverse event who had also taken more doses than prescribed, in addition to taking the doses too close together.

Adverse events reported as being associated with the administration of the patient's second dose before 2.5 hours included CNS, gastrointestinal, respiratory, genitourinary, and cardiovascular effects, such as CNS depression, dizziness, seizure, confusion, delirium, difficulty awakening, drowsiness, falls, nausea, vomiting, respiratory depression, bedwetting, and bradycardia. In at least four case reports, it was noted that the event scared the patient to the point that they either considered or did reportedly stop taking Xyrem for fear that the error would occur again. In another case, the patient became fearful after realizing she had taken her dose too soon and forced herself to throw up and remain awake as long as she could to ensure that she was breathing.

Case Examples: second dose taken too early (adverse event)

ID #14800123:

A 65-year-old male patient was prescribed 4.5 g BID of Xyrem nightly for narcolepsy. On an unknown date in April 2018, the patient was tired when preparing his doses. He ran out of medication in his current bottle when drawing up doses. He went to get a new bottle to finish drawing up his doses, got distracted, and put both doses in one container. He realized what he had done when he took his dose as it was too salty and the other dose was too clear. He tasted the other dose, and it was just water. His wife took him to the hospital for observation. He drank a lot of water on the way, and the hospital also gave him fluids. His breathing rate, heart rate, and blood pressure had gone down (heart rate in the 40s). The patient stayed overnight in the hospital. He woke up 3.5 hours later and felt groggier and sleepier than usual.

ID #15992034:

A 55-year-old female patient was prescribed Xyrem 4.5 g BID nightly for narcolepsy. On an unknown date in 2019, the patient took her first dose and then got distracted. She ended up doing something with her daughter, then she was talking with her husband. When she went back to her bed, she forgot she had already taken her first dose and took her second dose (15 min. apart). Patient called the poison center and 911. Shortly after emergency medical services (EMS) left, the patient started convulsing, so 911 was called again. EMS took her to the hospital, and she was intubated. Patient was worried about taking Xyrem again.

Of the 32 patients with a reported adverse event associated with the misadministration of their second dose, most (n=19, 59%) had administered their second dose 1 hour or less than their first dose. Only two patients reported that this type of error had occurred more than once, and the majority (84%) of the descriptions noted that the wrong frequency administration was accidental. Compared to the 24 patients with no reported associated adverse event, most (n=18, 75%) had administered their second dose between 1 and 2.5 hours after their second dose, half (50%) reported that this type of error had occurred on more than one

occasion, and about one-third (29%) described the misadministration as intentional, with 58% of the cases unclear if Xyrem or Xywav had been intentionally or accidentally administered at the wrong frequency.

Case Examples: second dose taken too early (no adverse event reported)

ID #12436789:

A 49-year-old male patient was prescribed 4.5 g BID of Xyrem nightly for narcolepsy with cataplexy. The patient's wife reported that on October 30, 2015, the patient accidentally took his second dose only 1 hour after his first dose. At 11:30 pm, the patient took his first dose and forgot to reset his alarm. At 12:30 am, the alarm went off, which was the normal time he takes his second dose, and the patient accidentally took his second dose only 1 hour after the first dose. No adverse events were reported.

ID #12351728:

A female patient of unknown age was prescribed 3 g BID nightly of Xyrem for narcolepsy with cataplexy. The patient reported that about once a week (year unknown) she would take her second dose about 1.5 hours after the first dose because Xyrem wouldn't allow her to fall asleep with the first dose for a couple of hours and the second dose would take until 4 am before it works. The nurse mentioned that the patient had been counseled to wait at least 2.5 hours.

Many of the case reports describing an error in which the patient took their dose too early didn't provide information regarding why it occurred, but in those reports that did, several contributing factors were noted, with the most common related to being distracted, forgetting, not checking their clock when they awoke, and intentional misuse:

- Distracted, forgot, and/or restarted routine
- Sleepwalking
- Didn't check alarm clock when woke up to take second dose (just assumed it was the correct time to take it)
- Schedule changed and didn't readjust alarm clock or when to appropriately take the second dose
- Intentionally administered too early as first dose wasn't working/not falling asleep or worked better with schedule
- Misunderstanding of the frequency prescribed or misread the directions
- Not recognizing that they had prepared two doses in the same container as medication solution is clear

Second dose taken too late (more than 4 hours after the first dose) or not taken at all

Six (9%) of the 65 case reports involved patients taking their second dose of Xyrem or Xywav more than 4 hours later. In most (67%) of these cases, the exact timing of when the second dose was administered was unknown. In the two cases that did mention the number of hours, one patient had administered the second dose 4.75 hours after the first dose and another patient had taken it 5.5 hours later.

Two-thirds (67%) of the six reports were described as accidental, with one-third (33%) considered unknown if the patient had accidentally or intentionally administered their second dose at the wrong time. Most of these six reports (67%) also described the patient taking their second dose more than 4 hours later on multiple occasions, with only two of the cases (33%) describing it as a single event.

None of the "too late" frequency errors described a serious adverse event that was associated as occurring due to the misadministration. One patient did indicate that they woke up lightheaded with nausea after taking their dose more than the recommended four hours after the first dose. This same patient also stated that because he had taken his dose too late at 5 am, he drove to work that same morning less than 6 hours after taking his second dose (see **case example** below).

Case Example: second dose taken too late

ID #19801207:

A 34-year-old male patient was prescribed Xyrem 2.25 g BID nightly for narcolepsy. On an unknown date in September 2017, the patient's alarm clock didn't go off. He woke up thinking it was 2 am and took his second dose, but it was actually 5 am. The patient later woke up at 7 am to get ready for work and was lightheaded and had nausea. He didn't wait 6 hours before driving to work that day.

Seven of the 65 total case reports that were evaluated mentioned more than one wrong frequency error in which there were instances when they took their second dose too early or too late and also instances in which they didn't take their second dose at all. Almost all (n=5, 71%) reported that not taking their second dose occurred on multiple occasions. None of these patients reported any serious harm that appeared to be associated with not taking their second Xyrem or Xywav dose.

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Case Example: second dose not taken at all

ID #14821352:

A 24-year-old female patient reported that she didn't always take her 2nd dose of Xyrem at night (2.25 g BID), due to having trouble waking up at night after taking the first dose. Her alarm clock didn't wake her, nor could her husband wake her. After speaking with her doctor, the dose was lowered to 2 g BID.

While the reason for taking the second dose of Xyrem or Xywav too late, or not at all, was not always mentioned, contributing factors that were noted in some of the reports were most commonly associated with use of an alarm clock and not waking up in time, which in a least one case may have been related to the dose prescribed. Identified contributing factors included:

- Didn't hear alarm clock or turned alarm clock off (couldn't wake up)
- Set alarm clock wrong (PM vs. AM), or alarm clock didn't go off
- Forgot
- Couldn't take second dose as patient woke up too close to when they needed to drive
- Sleep pattern disrupted due to other medical condition

Limitations

This analysis of 65 wrong frequency error cases associated with the use of Xyrem or Xywav was limited to the information provided in the FAERS reports, which may have been incomplete or inaccurate as these reports may not be medically confirmed. Additionally, the interpretation of the information provided in each event description and the categorization of these errors may differ depending on the reviewer. As noted by FDA, these reports also do not establish causality and cannot be used to estimate an incidence rate. Thus, the actual occurrence of these types of errors cannot be determined. In general, though, medication errors tend to be underreported. This evaluation only reviewed a subset of reports associated with Xyrem or Xywav use; further searches may identify additional wrong frequency errors.

Conclusion

Based on the FAERS reports that were included for analysis as a part of this review, wrong frequency errors may occur in patients who are prescribed immediate-release sodium oxybate or other oxybate salts, in which they either take their second dose too early (less than 2.5 hours after the first dose), too late (more than 4 hours after the first dose), or not at all.

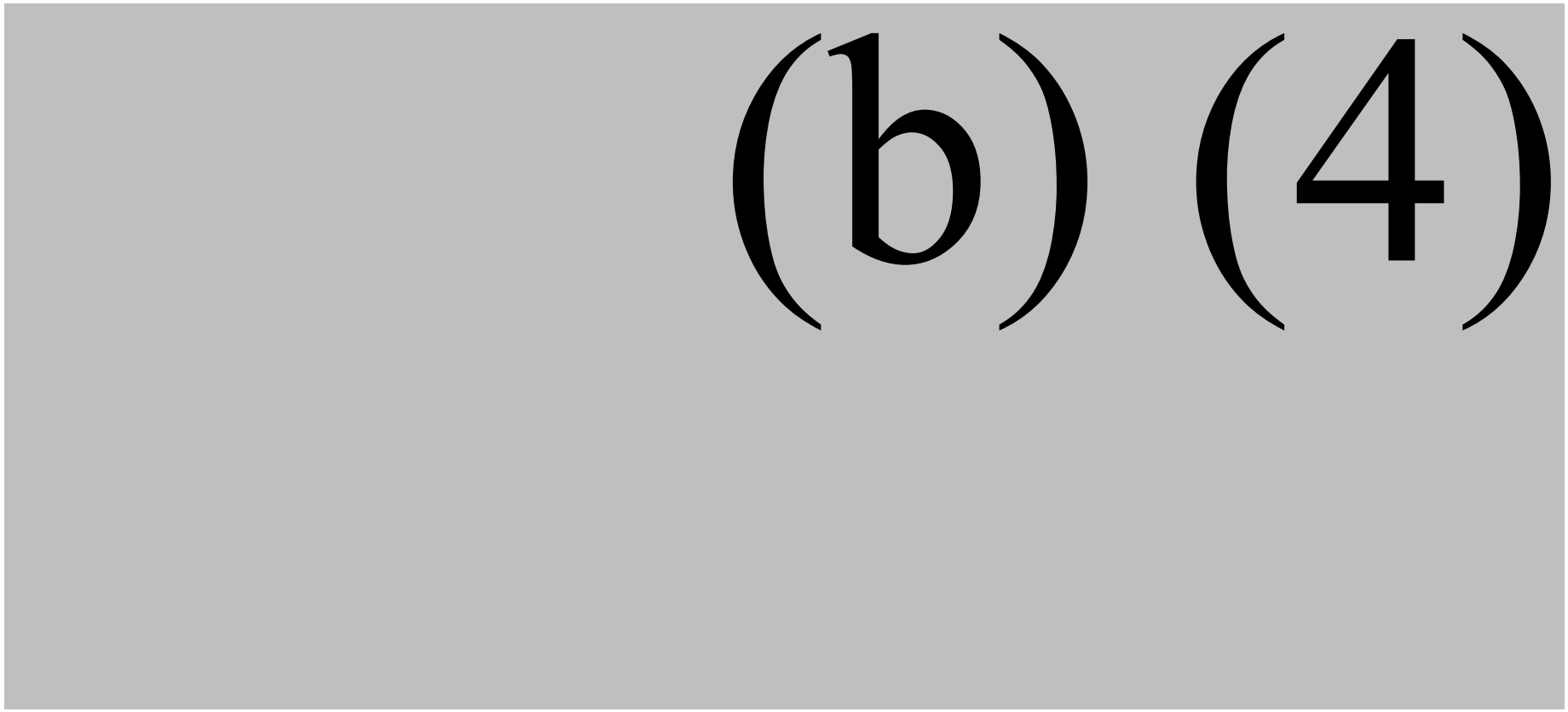
Harm was reported more frequently when patients took their second dose too early, particularly when taken 1 hour or less after their first dose, compared to errors in which the second dose was taken more than 4 hours later or not at all. Such adverse events included CNS depression, dizziness, seizure, confusion, delirium, difficulty awakening, drowsiness, falls, nausea, vomiting, respiratory depression, bedwetting, and bradycardia. In about one-third of all reviewed cases, the event resulted in an ED visit or admission to the hospital for monitoring and/or intervention. As described in a few reports, harm can also occur if the error causes the patient to want to discontinue therapy, for fear that the error and resulting adverse event will occur again.

Multiple contributing factors have been reported as being associated with errors in which the second dose was administered too soon, including: distracted, forgot, and/or restarted routine; sleepwalking; didn't check or readjust the alarm clock to make sure that enough time had passed; intentionally administered second dose too early as first dose not working to fall asleep; misunderstood frequency prescribed by provider or misread directions; and not recognizing that two doses were added to the same container as the medication is a clear solution.

While harmful events were not reported as being associated with errors in which the second dose was taken more than 4 hours after the first dose or not taken at all, as described in one case, this could result in dangerous situations in which the patient may choose to drive to work or operate other machinery less than 6 hours after the second dose has been administered. Contributing factors noted with these reported events included: forgot, didn't hear alarm clock and couldn't get up, set alarm clock wrong or alarm didn't go off, couldn't take second dose as woke up too close to when needed to drive, and disrupted sleep pattern due to other condition.

Further analysis of these reports may be warranted for consideration of possible inclusion in product labeling and/or REMS materials.

About (b) (4)



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ORIGINAL ARTICLE

Efficacy and safety of calcium, magnesium, potassium, and sodium oxybates (lower-sodium oxybate [LXB]; JZP-258) in a placebo-controlled, double-blind, randomized withdrawal study in adults with narcolepsy with cataplexy

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Clinical trial: A Study of the Efficacy and Safety of JZP-258 in Subjects With Narcolepsy With Cataplexy; https://clinicaltrials.gov/ct2/show/NCT03030599, ClinicalTrials.gov identifier: NCT03030599

Abstract

Study Objectives: Evaluate efficacy and safety of lower-sodium oxybate (LXB), a novel oxybate medication with 92% less sodium than sodium oxybate (SXB).
Methods: Adults aged 18–70 years with narcolepsy with cataplexy were eligible. The study included a ≤30-day screening period; a 12-week, open-label, optimized treatment and titration period to transition to LXB from previous medications for the treatment of cataplexy; a 2-week stable-dose period (SDP); a 2-week, double-blind, randomized withdrawal period (DBRWP); and a 2-week safety follow-up. During DBRWP, participants were randomized 1:1 to placebo or to continue LXB treatment.
Results: Efficacy was assessed in 134 participants who received randomized treatment, and safety was assessed in all enrolled participants ($N = 201$). Statistically significant worsening of symptoms was observed in participants randomized to placebo, with median (first quartile [Q1], third quartile [Q3]) change in weekly number of cataplexy attacks from SDP to DBRWP (primary efficacy endpoint) in the placebo group of 2.35 (0.00, 11.61) versus 0.00 (−0.49, 1.75) in the LXB group ($p < 0.0001$; mean [standard deviation, SD] change: 11.46 [24.751] vs 0.12 [5.772]), and median (Q1, Q3) change in Epworth Sleepiness Scale score (key secondary efficacy endpoint) of 2.0 (0.0, 5.0) in the placebo group versus 0.0 (−1.0, 1.0) in the LXB group ($p < 0.0001$; mean [SD] change: 3.0 [4.68] vs 0.0 [2.90]). The most common treatment-emergent adverse events with LXB were headache (20.4%), nausea (12.9%), and dizziness (10.4%).
Conclusions: Efficacy of LXB for the treatment of cataplexy and excessive daytime sleepiness was demonstrated. The safety profile of LXB was consistent with SXB.
Clinical trial registration: NCT03030599.

Statement of Significance

Lower-sodium oxybate (LXB), a medication approved in the United States for the treatment of cataplexy and excessive daytime sleepiness (EDS) in participants with narcolepsy, contains the same active moiety as sodium oxybate (SXB) with 92% less sodium. SXB is recommended as a standard of care for the treatment of narcolepsy symptoms by the American Academy of Sleep Medicine, European Federation of Neurological Societies, and the French consensus group. This double-blind randomized withdrawal study evaluated the efficacy and safety of LXB. Cataplexy attacks and EDS worsened significantly in those assigned to placebo but remained stable in those who continued LXB treatment, demonstrating the efficacy of LXB. The overall safety profile of LXB was as expected based on prior experience with SXB.

Key words: narcolepsy; cataplexy; excessive daytime sleepiness; sodium oxybate; JZP-258

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Original Article

ORIGINAL ARTICLE

Long-term compliance, safety, and tolerability of sodium oxybate treatment in patients with narcolepsy type 1: a postauthorization, noninterventional surveillance study

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Work Performed: Multiple study centers.

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Abstract

Study Objectives: To evaluate adherence to sodium oxybate prescribing information for indication and dosage, patients' compliance with instructions for use, safety/tolerability in routine clinical practice, and abuse potential.

Methods: A postauthorization, noninterventional surveillance study (NCT00244465) in patients who were prescribed sodium oxybate according to current practice by sleep disorders specialists. Patients were monitored for ≤18 months.

Results: Overall, 749 patients were enrolled; 730 included in the intent-to-treat population (narcolepsy type 1 $n = 670$, other indications $n = 60$). We report on patients with narcolepsy type 1 (female 47.9%, mean age 39.4 years); 495/670 (73.9%) completed the study. Median dose: at start of study 4.5 g per night, 6 g per night throughout study, in two equal doses. According to the treatment compliance checklist, 35.5 per cent of patients consumed alcohol, 19.3 per cent took the medication <2 hr after food, and 27.1 per cent did not adhere to recommended time schedule, with few associated treatment-emergent adverse events (TEAEs). Incidences of higher-than-recommended doses, difficulty in preparing doses, and abuse were low. TEAEs were reported by 67.3 per cent, most frequently headache (11.6%) and nasopharyngitis (6.4%). Discontinuation due to TEAEs: 8.8 per cent. Serious TEAEs: 6.4 per cent. There were no reports of respiratory depression. No particular safety concerns were identified in pediatric or elderly patients, or those with underlying sleep apnea.

Conclusions: In this large postauthorization safety study of sodium oxybate use, indication and dosage prescribing recommendations were generally followed, and most patients complied with instructions, with deviations around alcohol consumption, eating before dosing and timing. The overall safety profile was consistent with previous observations; incidence of abuse was low.

Section: Neurological disorders.

Clinical Trial: Postauthorization, noninterventional, surveillance, pharmacoepidemiology study to evaluate long-term safety, tolerability, and compliance in administration of Xyrem (sodium oxybate) oral solution in patients who receive treatment with this medication in regular clinical practice. https://clinicaltrials.gov/ct2/show/NCT00244465, ClinicalTrials.gov: NCT00244465.

Statement of Significance

Sodium oxybate is an effective drug for reducing cataplexy attacks and excessive daytime sleepiness in patients with narcolepsy. Administration of sodium oxybate presents some practical challenges, including dose titration, twice nightly administration, and need for abstinence from alcohol. This was the largest postauthorization, noninterventional surveillance study of patients with narcolepsy conducted to date. It provides important long-term, real-world data on the use of sodium oxybate in clinical practice across Europe. Prescribing recommendations were generally followed, and most patients complied with instructions. No new safety concerns were identified. The incidence of abuse was low.

Key Words: sodium oxybate; narcolepsy; narcolepsy—pharmacotherapy; pediatrics—narcolepsy; postauthorization study; compliance

Submitted: 20 December, 2017; **Revised:** 11 May, 2018