ONCE AT BEDTIME

Lumryz™ (sodium oxybate) for extended-release oral suspension Ⓒ 4.5 | 6 | 7.5 | 9 g

MAJOR CONTRIBUTION TO PATIENT CARE[1]
FDA, OCTOBER 2024

The only single-dose oxybate for the treatment of excessive daytime sleepiness (EDS) and cataplexy in patients 7 years of age and older with narcolepsy.[2]

Dosing & titration guide

Manage expectations for your switch and start patients.

- **Currently taking twice-nightly oxybate**
- **New to oxybate or previous oxybate history**

INDICATIONS AND USAGE

LUMRYZ (sodium oxybate) for extended-release oral suspension is a central nervous system depressant indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.

IMPORTANT SAFETY INFORMATION

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

Central Nervous System Depression

LUMRYZ™ (sodium oxybate) is a CNS depressant. Clinically significant respiratory depression and obtundation may occur in patients treated with LUMRYZ at recommended doses. Many patients who received LUMRYZ during clinical trials in narcolepsy were receiving CNS stimulants.

Abuse and Misuse

LUMRYZ (sodium oxybate) is the sodium salt of gamma-hydroxybutyrate (GHB). Abuse or misuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreased consciousness, coma, and death.

Because of the risks of CNS depression and abuse and misuse, LUMRYZ is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the LUMRYZ REMS.

CONTRAINDICATIONS

LUMRYZ is contraindicated for use in:

- combination with sedative hypnotics or alcohol
- patients with succinic semialdehyde dehydrogenase deficiency

WARNINGS AND PRECAUTIONS

Central Nervous System Depression

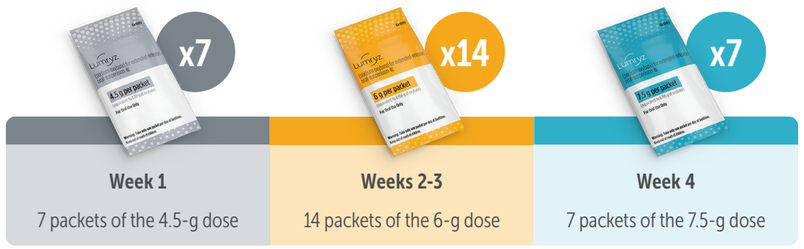
The concurrent use of LUMRYZ with other CNS depressants, including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating antiepileptic drugs, general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death. If use of these CNS depressants in combination with LUMRYZ is required, dose reduction or discontinuation of one or more CNS depressants (including LUMRYZ) should be considered. In addition, if short-term use of an opioid (eg, post- or perioperative) is required, interruption of treatment with LUMRYZ should be considered.

After first initiating treatment and until certain that LUMRYZ does not affect them adversely (eg, impair judgment, thinking, or motor skills), caution patients against engaging in hazardous activities requiring complete mental alertness or motor coordination such as operating hazardous machinery, including automobiles or airplanes. Also caution patients against engaging in these hazardous activities for at least six (6) hours after taking LUMRYZ. Patients should be queried about CNS depression-related events upon initiation of LUMRYZ therapy and periodically thereafter.

Please see additional Important Safety Information throughout, and full Prescribing Information, including BOXED Warning, and Medication Guide available at LUMRYZhcp.com.

The LUMRYZ Starter Kit is available for titrating new patients

Start appropriate patients with 28 days of treatment in escalating dose strengths.[2]



Each premeasured packet contains a full therapeutic dose.[2]

No middle-of-the-night alarm clock[2-4]

Convenient for packing and travel

No second dose left out unattended[2-4]

Taken orally as a single dose at bedtime[2]

- Can be taken concomitantly with alerting agents

Each dose contains a blend of immediate- and controlled-release granules[2,5]

- Shake for 60 seconds—expect the granules to not fully dissolve in water* and have a gritty texture with a salty taste[6]

Should be taken at least 2 hours after eating and in bed[2]

- Patients may fall asleep within 5-15 minutes of taking their dose without feeling drowsy

***Do not use hot water.**

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use) for full administration instructions.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Abuse and Misuse

LUMRYZ is a Schedule III controlled substance. The active ingredient of LUMRYZ, sodium oxybate, is the sodium salt of gamma-hydroxybutyrate (GHB), a Schedule I controlled substance. Abuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death. The rapid onset of sedation, coupled with the amnestic features of GHB, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (eg, assault victim). Physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely.

LUMRYZ REMS

LUMRYZ is available only through a restricted distribution program called the LUMRYZ REMS because of the risks of central nervous system depression and abuse and misuse.

Notable requirements of the LUMRYZ REMS include the following:

- Healthcare providers who prescribe LUMRYZ are specially certified.
- LUMRYZ will be dispensed only by pharmacies that are specially certified.
- LUMRYZ will be dispensed and shipped only to patients who are enrolled in the LUMRYZ REMS with documentation of safe use conditions.

Further information is available at www.LUMRYZREMS.com or by calling 1-877-453-1029.

Please see additional Important Safety Information throughout, and full Prescribing Information, including BOXED Warning, and Medication Guide available at LUMRYZhcp.com.

Managing expectations for patients

Patients who are new to oxybate or who have discontinued oxybate treatment may have questions during their first few weeks of treatment with LUMRYZ.

Everyone responds to treatment differently

It may take time before your patients can see a difference in their EDS or cataplexy.

In the clinical trial for LUMRYZ, some participants saw significant symptom improvements as early as week 3, while others saw symptom improvements at week 13 after titrating to a higher dose.[2,5†]

Finding their stable dose takes time

It may take time to find the dose that best balances efficacy and tolerability for each patient.

In the clinical trial for LUMRYZ, side effects typically occurred when participants started a new dose. Generally, the side effects then declined over time while staying on the same dose.[5]

Consider frequent check-ins in the titration period

Encourage patients to share their experience with LUMRYZ to help determine if they might benefit from any adjustments to their dose.

†As seen in participants taking the 9-g dose of LUMRYZ and compared to baseline results at the start of the trial.

The most common side effects reported by participants in the clinical trial include nausea, dizziness, enuresis, headache, and vomiting. In pediatric patients, the most common side effects include nausea, enuresis, vomiting, headache, weight decreased, decreased appetite, dizziness, and sleepwalking.[2]

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Respiratory Depression and Sleep-Disordered Breathing

LUMRYZ may impair respiratory drive, especially in patients with compromised respiratory function. In overdoses of oxybate with illicit use of GHB, life-threatening respiratory depression has been reported. Increased apnea and reduced oxygenation may occur with LUMRYZ administration. A significant increase in the number of central apneas and clinically significant oxygen desaturation may occur in patients with obstructive sleep apnea treated with LUMRYZ. Prescribers should be aware that sleep-related breathing disorders tend to be more prevalent in obese patients, in men, in postmenopausal women not on hormone replacement therapy, and among patients with narcolepsy.

Depression and Suicidality

Depression, and suicidal ideation and behavior, can occur in patients treated with LUMRYZ. In an adult clinical trial in patients with narcolepsy (n=212), there were no suicide attempts, but one patient with a history of depression and anxiety developed suicidal ideation in the LUMRYZ-treated group. In a clinical trial in pediatric narcolepsy patients administered immediate-release sodium oxybate, one patient experienced suicidal ideation and two patients reported depression. The emergence of depression in patients treated with LUMRYZ requires careful and immediate evaluation. Patients with a previous history of a depressive illness and/or a suicide attempt should be monitored carefully for the emergence of depressive symptoms while taking LUMRYZ.

Other Behavioral or Psychiatric Adverse Reactions

Other behavioral and psychiatric adverse reactions can occur in patients taking LUMRYZ. During adult clinical trials in patients with narcolepsy administered LUMRYZ, 2% of 107 patients treated with LUMRYZ experienced a confusional state. No patients treated with LUMRYZ discontinued treatment because of confusion. Anxiety occurred in 7.5% of 107 patients treated with LUMRYZ in the adult trial in patients with narcolepsy. Other psychiatric reactions reported in adult clinical trials in patients with narcolepsy administered LUMRYZ included irritability, emotional disorder, panic attack, agitation, delirium, and obsessive thoughts. Other neuropsychiatric reactions reported in adult clinical trials in patients with narcolepsy administered immediate-release sodium oxybate and in the postmarketing setting for immediate-release sodium oxybate include hallucinations, paranoia, psychosis, aggression, and agitation. In a clinical trial in pediatric patients administered immediate-release sodium oxybate, neuropsychiatric reactions including acute psychosis, confusion, and anxiety were reported. The emergence or increase in the occurrence of behavioral or psychiatric events in patients taking LUMRYZ should be carefully monitored.

Parasomnias

Parasomnias can occur in patients taking LUMRYZ. Sleepwalking, defined as confused behavior occurring at night and at times associated with wandering, was reported in 3% of 107 adult patients with narcolepsy treated with LUMRYZ. No patients treated with LUMRYZ discontinued due to sleepwalking. Episodes of sleepwalking should be fully evaluated and appropriate interventions considered.

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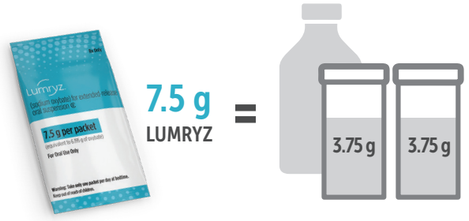
DOSING IN ADULTS

How might once-at-bedtime LUMRYZ make an impact for your patients' daytime?

SWITCH from twice-nightly oxybate

Select the nearest equivalent dose of LUMRYZ[2]

For example, 7.5 g of LUMRYZ is approximately 2 doses of 3.75-g twice-nightly sodium oxybate.



IMPORTANT FOR SWITCH PATIENTS

It's important to know **how often patients missed the second dose of their twice-nightly oxybate**, as it may be more appropriate to switch to a lower starting dose of LUMRYZ than what they were previously prescribed. **It may take time to find a stable dose. Remind patients** it's important to share how they are feeling with your office during the titration process.

START patients new to oxybate or with previous oxybate history

Consider increasing the recommended starting dose of 4.5 g by 1.5 g per night at frequent intervals based on efficacy and tolerability.[2]

Doses higher than 9 g per night have not been studied and should not ordinarily be administered.[2]

IMPORTANT FOR STARTING LUMRYZ

Patients will start with the smallest dose, then adjust the strength up or down, slowly over time, based on efficacy and tolerability.[2,7] It's important to let patients know that everybody responds to treatment differently and it may take time before they can see a difference in their EDS or cataplexy as their body adjusts to the medicine.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Use in Patients Sensitive to High Sodium Intake

LUMRYZ has a high sodium content. In patients sensitive to sodium intake (eg, those with heart failure, hypertension, or renal impairment), consider the amount of daily sodium intake in each dose of LUMRYZ.

MOST COMMON ADVERSE REACTIONS

Most common adverse reactions (incidence ≥5% and greater than placebo) reported for any dose of LUMRYZ in a trial of adults with narcolepsy were nausea, dizziness, enuresis, headache, and vomiting. Similarly, in a trial of pediatric narcolepsy patients receiving immediate-release sodium oxybate, the most commonly observed adverse reactions (incidence ≥5%) were nausea, enuresis, vomiting, headache, decreased weight, decreased appetite, dizziness, and sleepwalking.

ADDITIONAL ADVERSE REACTIONS

Additional adverse reactions that occurred in ≥2% of adult patients with narcolepsy treated with LUMRYZ and were more frequent in the LUMRYZ treatment group than with placebo were vomiting, nausea, decreased weight, decreased appetite, dizziness, somnolence, headache, enuresis, anxiety, and somnambulism.

Please see additional Important Safety Information throughout, and full Prescribing Information, including BOXED Warning, and Medication Guide available at LUMRYZhcp.com.

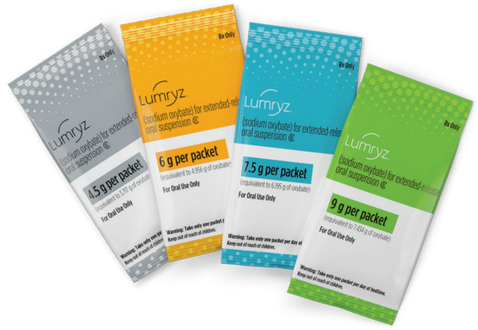
DOSING IN PEDIATRIC PATIENTS

Once-at-bedtime LUMRYZ is the only single-dose oxybate approved for pediatric use (ages ≥7)[2]

SWITCH pediatric patients ≥20 kg (44 lb)

Select the nearest equivalent dose of LUMRYZ[2]

Switch patients to LUMRYZ if they are taking a 4.5-g dose or higher of another sodium oxybate. The dosage may be gradually titrated based on efficacy and tolerability.



START pediatric patients ≥45 kg (99 lb)

Titrate gradually to a dose that best fits their needs[2]

Start on 4.5 g once per night and then increase by 1.5 g per night at weekly intervals to the maximum recommended dosage of 9 g per night orally.

What might it mean for family and care partners to **not wake to administer a middle-of-the-night dose?**

IMPORTANT SAFETY INFORMATION (cont'd)

DRUG INTERACTIONS

LUMRYZ is contraindicated for use in combination with alcohol or sedative hypnotics. Use of other CNS depressants may potentiate the CNS-depressant effects of LUMRYZ.

PREGNANCY AND LACTATION

There are no adequate data on the developmental risk associated with the use of sodium oxybate in pregnant women. LUMRYZ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. GHB is excreted in human milk after oral administration of sodium oxybate. There is insufficient information on the risk to a breastfed infant, and there is insufficient information on milk production in nursing mothers. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUMRYZ and any potential adverse effects on the breastfed infant from LUMRYZ or from the underlying maternal condition.

PEDIATRIC USE

LUMRYZ has not been studied in a pediatric clinical trial for narcolepsy. The safety and effectiveness of LUMRYZ in the treatment of cataplexy or excessive daytime sleepiness in pediatric patients 7 years of age and older with narcolepsy is supported by evidence from a double-blind, placebo-controlled, randomized-withdrawal study of immediate-release sodium oxybate. Safety and effectiveness of LUMRYZ in pediatric patients below the age of 7 years have not been established.

GERIATRIC USE

Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

HEPATIC IMPAIRMENT

LUMRYZ should not be initiated in patients with hepatic impairment because appropriate dosage adjustments for initiation cannot be made with the available dosage strengths. Patients with hepatic impairment who have been titrated to a maintenance dosage of another oxybate product can be switched to LUMRYZ if the appropriate dosage strength is available.

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LUMRYZ is a single-dose oxybate for the treatment of EDS and cataplexy in patients 7 years of age and older with narcolepsy.[2]

MAJOR CONTRIBUTION TO PATIENT CARE[1]
FDA, OCTOBER 2024

WHY "1" MATTERS

The FDA found once-nightly dosing promotes normal nighttime sleep.[8]

"The benefits of LUMRYZ once-nightly dosing rise to the level of making a major contribution to patient care because LUMRYZ dosing provides an opportunity to **MINIMIZE SLEEP FRAGMENTATION AND DISRUPTION OF SLEEP ARCHITECTURE** in a way that is not possible for a patient on a twice-nightly dosing regimen of oxybate.

This is medically relevant because the goal for treating patients with sleep disorders is to **RESTORE A NORMAL SLEEP PATTERN AND A HEALTHIER SLEEP PHYSIOLOGY.**

Aside from the medical benefits of not having to awaken to take a second dose, it is inherently **MORE CONVENIENT, EASIER, AND LESS BURDENSOME** for patients to forgo awakening to take a second dose on a nightly basis."[1]

Due to these findings, the FDA has determined LUMRYZ dosing to be clinically superior* to twice-nightly oxybates.

"Importantly, this is in the context of a chronic neurological condition that requires potentially lifelong treatment."[1]

-FDA Clinical Superiority Findings, October 2024*

To get started, enroll your patient in RYZUP™ Support Services.
Scan or visit RYZUPSupport.com/iassist

*Based on a determination of Orphan Drug Exclusivity by the FDA Office of Orphan Products Development between LUMRYZ and XYREM® or XYWAV®. There are no head-to-head data for LUMRYZ and XYREM or XYWAV.

IMPORTANT SAFETY INFORMATION (cont'd)

DEPENDENCE AND TOLERANCE

There have been case reports of withdrawal, ranging from mild to severe, following discontinuation of illicit use of GHB at frequent repeated doses (18 g to 250 g per day) in excess of the recommended dosage range. Signs and symptoms of GHB withdrawal following abrupt discontinuation included insomnia, restlessness, anxiety, psychosis, lethargy, nausea, tremor, sweating, muscle cramps, tachycardia, headache, dizziness, rebound fatigue and sleepiness, confusion, and, particularly in the case of severe withdrawal, visual hallucinations, agitation, and delirium. These symptoms generally abated in three (3) to fourteen (14) days. In cases of severe withdrawal, hospitalization may be required. The discontinuation effects of LUMRYZ have not been systematically evaluated in controlled clinical trials.

Tolerance to LUMRYZ has not been systematically studied in controlled clinical trials. There have been some case reports of symptoms of tolerance developing after illicit use at dosages far in excess of the recommended LUMRYZ dosage regimen.

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References: 1. US Food and Drug Administration. Clinical superiority findings. Accessed October 16, 2024. https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/clinical-superiority-findings#67112edcdbcc0 **2.** LUMRYZ™ (sodium oxybate for extended-release oral suspension). Prescribing Information. Chesterfield, MO: Avadel Pharmaceuticals. **3.** XYREM. Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc; 2023. **4.** XYWAV. Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc; 2023. **5.** Kushida CA, Shapiro CM, Roth T, et al. Once-nightly sodium oxybate (FT218) demonstrated improvement of symptoms in a phase 3 randomized clinical trial in patients with narcolepsy. *Sleep.* 2022;45(6):1-11. **6.** LUMRYZ Instructions for Use. Chesterfield, MO: Avadel Pharmaceuticals; 2024. **7.** Caffrey AR, Borrelli EP. The art and science of drug titration. *Ther Adv Drug Saf.* 2020;11:2042098620958910. **8.** Avadel, Data on File.

Avadel™