LUMRYZ- sodium oxybate for suspension, extended release
LUMRYZ- sodium oxybate
Alkermes, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LUMRYZ® safely and effectively. See full prescribing information for LUMRYZ.

LUMRYZ (sodium oxybate) for extended-release oral suspension, CIII
Initial U.S. Approval: 2002

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

See full prescribing information for complete boxed warning.

Central Nervous System Depression
• LUMRYZ is a CNS depressant, and respiratory depression can occur with LUMRYZ use (5.1, 5.4)
Abuse and Misuse
• LUMRYZ 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)
LUMRYZ is available only through a restricted program called the LUMRYZ REMS (5.3)

RECENT MAJOR CHANGES

Dosage and Administration (2.3) 11/2025

INDICATIONS AND USAGE

LUMRYZ 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 (1).

DOSAGE AND ADMINISTRATION

Dosing for Adults:
- Initiate dosage at 4.5 g once per night orally (2.1).
- Titrate to effect in increments of 1.5 g per night at weekly intervals (2.1).
- Recommended dosage range: 6 g to 9 g once per night orally (2.1).

Dosing for Pediatric Patients (7 Years of Age and Older):
- The recommended starting dosage, titration regimen, and maximum total nightly dosage are based on body weight (2.2)
- *Pediatric patients 7 years and older* ***weighing at least 45 kg***: The recommended starting dosage is 4.5 g once per night. Increase the dosage by 1.5 g per night at weekly intervals to the maximum recommended dosage of 9 g once per night orally. The dosage may be gradually titrated based on efficacy and tolerability (2.2).
- *Pediatric patients 7 years and older* ***weighing less than 45 kg***: Because the recommended starting dosage cannot be achieved with the available strengths of LUMRYZ, use another sodium oxybate product to initiate treatment (2.2).

Important Administration Information
- Prepare the dose of LUMRYZ prior to bedtime; suspend dose in approximately ⅓ cup of water (with or without calorie-free drink mix or flavored water enhancer) in the mixing cup provided (2.3).
- Allow 2 hours after eating before dosing (2.3).
- Take LUMRYZ while in bed and lie down after dosing (2.3).

DOSAGE FORMS AND STRENGTHS

For extended-release oral suspension: Packets of 4.5 g, 6 g, 7.5 g, or 9 g (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 LUMRYZ 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 LUMRYZ

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 LUMRYZ: Monitor patients with heart failure, hypertension, or impaired renal function (5.8).

ADVERSE REACTIONS

Most common adverse reactions in adults (incidence ≥ 5% and greater than placebo) reported for any dose of LUMRYZ were nausea, dizziness, enuresis, headache, and vomiting (6.1).
Most common adverse reactions for pediatric patients (≥ 5%) in a study with immediate-release sodium oxybate were nausea, enuresis, vomiting, headache, weight decreased, decreased appetite, dizziness, and sleepwalking (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Alkermes, Inc. at 1-888-828-2335 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch***.**

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm (8.1).
- Geriatric patients: Monitor for impaired motor and/or cognitive function when taking LUMRYZ (8.5).
- Hepatic Impairment: Because of an increase in exposure, LUMRYZ should not be initiated in patients with hepatic impairment because appropriate dosage adjustments for initiation of LUMRYZ cannot be made (8.6).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING 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 *[see Warnings and Precautions (5.1)]*. Many patients who received sodium oxybate during clinical trials in narcolepsy were receiving central nervous system stimulants *[see Clinical Trials (14)]*.

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, decreases in the level of consciousness, coma, and death *[see Warnings and Precautions (5.2)]*.

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 *[see Warnings and Precautions (5.3)].*

1 INDICATIONS AND USAGE

LUMRYZ is indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.

2 DOSAGE AND ADMINISTRATION

2.1 Adult Dosing Information

The recommended starting dosage of LUMRYZ in adults is 4.5 grams (g) once per night administered orally. Increase the dosage by 1.5 g per night at weekly intervals to the recommended dosage range of 6 g to 9 g once per night orally. The dosage may be gradually titrated based on efficacy and tolerability. Doses higher than 9 g per night have not been studied and should not ordinarily be administered.

2.2 Pediatric Dosing Information

The recommended starting pediatric dosage, titration regimen, and maximum total nightly dosage are based on patient weight.

Pediatric Patients 7 years and Older Weighing at least 45 kg

The recommended starting dosage of LUMRYZ in pediatric patients 7 years and older weighing at least 45 kg is 4.5 g once per night administered orally. Increase the dosage by 1.5 g per night at weekly intervals to the maximum recommended dosage of 9 g once per night orally. The dosage may be gradually titrated based on efficacy and tolerability.

Pediatric Patients 7 years and Older Weighing Less than 45 kg

Because the recommended starting dosage in pediatric patients 7 years and older weighing less than 45 kg cannot be achieved with the available strengths of LUMRYZ, use another sodium oxybate product to initiate treatment. Refer to the Prescribing Information of other sodium oxybate products for the recommended dosage for those products.

The maximum recommended dosage for patients 7 years and older weighing 20 kg to <30 kg is 6 g once per night orally, and the maximum recommended dosage for patients 7 years and older weighing 30 kg to <45 kg is 7.5 g once per night orally [*see Dosage and Administration (2.4)*]. There is insufficient information to provide specific dosing recommendations for patients 7 years and older who weigh less than 20 kg.

2.3 Important Administration Instructions

LUMRYZ is taken orally as a single dose at bedtime. Prepare the dose of LUMRYZ prior to bedtime. Prior to ingestion, the dose of LUMRYZ should be suspended in approximately 1/3 cup (approximately 80 mL) of water (with or without calorie-free drink mix or flavored water enhancer) in the mixing cup provided *[see Instructions for Use]*. Do not use hot water *[see Clinical Pharmacology (12.3)]*. After mixing, consume LUMRYZ within 30 minutes.

Take LUMRYZ at least 2 hours after eating *[see Clinical Pharmacology (12.3)].*

Patients should take LUMRYZ while in bed and lie down immediately after dosing as LUMRYZ may cause them to fall asleep abruptly without first feeling drowsy. Patients will often fall asleep within 5 minutes of taking LUMRYZ, and will usually fall asleep within 15 minutes, though the time it takes any individual patient to fall asleep may vary from night to night. Patients should remain in bed following ingestion of LUMRYZ.

2.4 Switching Patients from Immediate-Release Sodium Oxybate

Patients who are currently being treated with immediate-release sodium oxybate may be switched to LUMRYZ at the nearest equivalent dosage in grams per night (e.g., 7.5 g sodium oxybate divided into two 3.75 g doses per night to 7.5 g LUMRYZ once per night).

3 DOSAGE FORMS AND STRENGTHS

For extended-release oral suspension: LUMRYZ is a white to off-white powder provided in packets of 4.5 g, 6 g, 7.5 g, or 9 g of sodium oxybate.

4 CONTRAINDICATIONS

LUMRYZ is contraindicated for use in:

- combination with sedative hypnotics *[see Warnings and Precautions (5.1)]*
- combination with alcohol *[see Warnings and Precautions (5.1)]*
- patients with succinic semialdehyde dehydrogenase deficiency *[see Clinical Pharmacology (12.3)]*

5 WARNINGS AND PRECAUTIONS

5.1 Central Nervous System Depression

LUMRYZ is a central nervous system (CNS) depressant. Clinically significant respiratory depression and obtundation has occurred in patients treated with immediate-release sodium oxybate at recommended doses in clinical trials and may occur in patients treated with LUMRYZ at recommended doses. LUMRYZ is contraindicated in combination with alcohol and sedative hypnotics. 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 (e.g., post- or perioperative) is required, interruption of treatment with LUMRYZ should be considered. In addition to coadministration of LUMRYZ and alcohol being contraindicated because of respiratory depression, consumption of alcohol while taking LUMRYZ may also result in a more rapid release of the dose of sodium oxybate *[see Clinical Pharmacology (12.3)]*.

Healthcare providers should caution patients about operating hazardous machinery, including automobiles or airplanes, until they are reasonably certain that LUMRYZ does not affect them adversely (e.g., impair judgment, thinking, or motor skills). Patients should not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery or a motor vehicle or flying an airplane, for at least 6 hours after taking LUMRYZ. Patients should be queried about CNS depression-related events upon initiation of LUMRYZ therapy and periodically thereafter.

LUMRYZ is available only through a restricted program under a REMS *[see Warnings and Precautions (5.3)].*

5.2 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 (e.g., assault victim). Because illicit use and abuse of GHB have been reported, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of GHB (e.g., increase in size or frequency of dosing, drug-seeking behavior, feigned cataplexy) *[see Warnings and Precautions (5.3) and Drug Abuse and Dependence (9.2)].*

LUMRYZ is available only through a restricted program under a REMS *[see Warnings and Precautions (5.3)].*

5.3 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 *[see Warnings and Precautions (5.1, 5.2)]*.

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.

5.4 Respiratory Depression and Sleep-Disordered Breathing

LUMRYZ may impair respiratory drive, especially in patients with compromised respiratory function. In overdoses of oxybate and with illicit use of GHB, life-threatening respiratory depression has been reported *[see Overdosage (10)]*.

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.

During polysomnographic evaluation (PSG), central sleep apnea and oxygen desaturation were observed in pediatric patients with narcolepsy treated with immediate-release sodium oxybate.

In adult clinical trials of LUMRYZ in patients with narcolepsy, no subjects with apnea/hypopnea indexes greater than 15 were allowed to enroll.

In an adult study assessing the respiratory-depressant effects of immediate-release sodium oxybate at doses up to 9 g per night in 21 patients with narcolepsy, no dose-related changes in oxygen saturation were demonstrated in the group as a whole. One of four patients with preexisting moderate-to-severe sleep apnea had significant worsening of the apnea/hypopnea index during treatment.

In an adult study assessing the effects of immediate-release sodium oxybate 9 g per night in 50 patients with obstructive sleep apnea, immediate-release sodium oxybate did not increase the severity of sleep-disordered breathing and did not adversely affect the average duration and severity of oxygen desaturation overall. However, there was a significant increase in the number of central apneas in patients taking immediate-release sodium oxybate, and clinically significant oxygen desaturation (≤55%) was measured in three patients (6%) after administration, with one patient withdrawing from the study and two continuing after single brief instances of desaturation.

In adult clinical trials in 128 patients with narcolepsy administered immediate-release sodium oxybate, two subjects had profound CNS depression, which resolved after supportive respiratory intervention. Two other patients discontinued immediate-release sodium oxybate because of severe difficulty breathing and an increase in obstructive sleep apnea. In two controlled trials assessing polysomnographic (PSG) measures in adult patients with narcolepsy administered immediate-release sodium oxybate, 40 of

477 patients were included with a baseline apnea/hypopnea index of 16 to 67 events per hour, indicative of mild to severe sleep-disordered breathing. None of the 40 patients had a clinically significant worsening of respiratory function, as measured by apnea/hypopnea index and pulse oximetry at doses of 4.5 g to 9 g per night.

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. Increased central apneas and clinically relevant desaturation events have been observed with immediate-release sodium oxybate administration in adult and pediatric patients.

5.5 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 administered LUMRYZ *[see Adverse Reactions (6.1)]*, there were no suicide attempts, but one patient developed suicidal ideation at the 9 g dose. In adult clinical trials in patients with narcolepsy (n=781) administered immediate-release sodium oxybate, there were two suicides and two attempted suicides in patients treated with immediate-release sodium oxybate, including three patients with a previous history of depressive psychiatric disorder. Of the two suicides, one patient used immediate-release sodium oxybate in conjunction with other drugs. Immediate-release sodium oxybate was not involved in the second suicide. Adverse reactions of depression were reported by 7% of 781 patients treated with immediate-release sodium oxybate, with four patients (<1%) discontinuing because of depression. In most cases, no change in immediate-release sodium oxybate treatment was required.

In a controlled trial in adults with narcolepsy administered LUMRYZ where patients were titrated from 4.5 g to 9 g per night, the incidences of depression were 0% at 4.5 g, 1% at 6 g, 1.1% at 7.5 g, and 1.3% at 9 g. In a controlled adult trial, with patients randomized to fixed doses of 3 g, 6 g, or 9 g per night immediate-release sodium oxybate or placebo, there was a single event of depression at the 3 g per night dose. In another adult controlled trial, with patients titrated from an initial 4.5 g per night starting dose of immediate-release sodium oxybate, the incidences of depression were 1.7%, 1.5%, 3.2%, and 3.6% for the placebo, 4.5 g, 6 g, and 9 g per night doses, respectively.

In a clinical trial in pediatric patients with narcolepsy (n=104) administered immediate-release sodium oxybate, one patient experienced suicidal ideation and two patients reported depression while taking immediate-release sodium oxybate.

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 suicide attempt should be monitored carefully for the emergence of depressive symptoms while taking LUMRYZ.

5.6 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. During adult clinical trials

in patients with narcolepsy administered immediate-release sodium oxybate, 3% of 781 patients treated with immediate-release sodium oxybate experienced confusion, with incidence generally increasing with dose.

No patients treated with LUMRYZ discontinued treatment because of confusion. Less than 1% of patients discontinued the immediate-release sodium oxybate because of confusion. Confusion was reported at all recommended doses of immediate-release sodium oxybate from 6 g to 9 g per night. In a controlled trial in adults where patients were randomized to immediate-release sodium oxybate in fixed total daily doses of 3 g, 6 g, or 9 g per night or placebo, a dose-response relationship for confusion was demonstrated, with 17% of patients at 9 g per night experiencing confusion. In that controlled trial, the confusion resolved in all cases soon after termination of treatment. In one trial where immediate-release sodium oxybate was titrated from an initial 4.5 g per night dose, there was a single event of confusion in one patient at the 9 g per night dose. In the majority of cases in all adult clinical trials in patients with narcolepsy administered immediate-release sodium oxybate, confusion resolved either soon after termination of dosing or with continued treatment.

Anxiety occurred in 7.5% of 107 patients treated with LUMRYZ in the adult trial in patients with narcolepsy. Anxiety occurred in 5.8% of the 874 patients receiving immediate-release sodium oxybate in adult clinical trials in another population.

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 with narcolepsy administered immediate-release sodium oxybate, neuropsychiatric reactions, including acute psychosis, confusion, and anxiety were reported while taking immediate-release sodium oxybate.

The emergence or increase in the occurrence of behavioral or psychiatric events in patients taking LUMRYZ should be carefully monitored.

5.7 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. Sleepwalking was reported in 6% of 781 patients with narcolepsy treated with immediate-release sodium oxybate in adult controlled and long-term open-label studies, with <1% of patients discontinuing due to sleepwalking. In controlled trials, rates of sleepwalking were similar for patients taking placebo and patients taking immediate-release sodium oxybate. It is unclear if some or all of the reported sleepwalking episodes correspond to true somnambulism, which is a parasomnia occurring during non-REM sleep, or to any other specific medical disorder. Five instances of sleepwalking with potential injury or significant injury were reported during a clinical trial of immediate-release sodium oxybate in patients with narcolepsy.

Parasomnias, including sleepwalking, have been reported in a pediatric clinical trial and in

postmarketing experience with immediate-release sodium oxybate. Therefore, episodes of sleepwalking should be fully evaluated, and appropriate interventions considered.

5.8 Use in Patients Sensitive to High Sodium Intake

LUMRYZ has a high sodium content. In patients sensitive to sodium intake (e.g., those with heart failure, hypertension, or renal impairment), consider the amount of daily sodium intake in each dose of LUMRYZ. Table 1 provides the approximate sodium content per LUMRYZ dose.

Table 1: Approximate Sodium Content per Total Nightly Dose of LUMRYZ (g = grams)

LUMRYZ Dose	Sodium Content/Total Nightly Exposure
4.5 g per night	820 mg
6 g per night	1100 mg
7.5 g per night	1400 mg
9 g per night	1640 mg

6 ADVERSE REACTIONS

The following clinically significant adverse reactions appear in other sections of the labeling:

- CNS Depression *[see Warnings and Precautions (5.1)]*
- Abuse and Misuse *[see Warnings and Precautions (5.2)]*
- Respiratory Depression and Sleep-Disordered Breathing *[see Warnings and Precautions (5.4)]*
- Depression and Suicidality *[see Warnings and Precautions (5.5)]*
- Other Behavioral or Psychiatric Adverse Reactions *[see Warnings and Precautions (5.6)]*
- Parasomnias *[see Warnings and Precautions (5.7)]*
- Use in Patients Sensitive to High Sodium Intake *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adult Patients

LUMRYZ was studied in one placebo-controlled trial (Study 1) *[see Clinical Studies (14.1)] in 212 patients with narcolepsy (107 patients treated with LUMRYZ and 105 with placebo).*

Adverse Reactions Leading to Treatment Discontinuation

In Study 1, 15.9% of patients treated with LUMRYZ discontinued because of adverse reactions, compared to 1.9% of patients receiving placebo. The most common adverse reaction leading to discontinuation was dizziness (4.7%). For LUMRYZ, 5.6% of patients discontinued due to adverse reactions on 4.5 g, 4.1% on 6 g, 4.5% on 7.5 g, and 3.9% on 9 g dose.

Most Common Adverse Reactions

The most common adverse reactions (incidence ≥5% and greater than placebo) reported for any dose of LUMRYZ were nausea, dizziness, enuresis, headache, and vomiting.

Adverse Reactions Occurring at an Incidence of 2% or Greater

Table 2 lists adverse reactions occurring in 2% or more of LUMRYZ-treated patients on any individual dose and at a rate greater than placebo-treated patients in Study 1.

Table 2: Adverse Reactions Occurring in 2% or More of LUMRYZ-Treated Adult Patients and Greater than for Placebo-Treated Patients in Study 1

Adverse Reaction	Placebo (N=105) %	LUMRYZ 4.5 g (N=107) %	LUMRYZ 6 g (N=97) %	LUMRYZ 7.5 g (N=88) %	LUMRYZ 9 g (N=77) %
Gastrointestinal Disorders					
Vomiting	2	3	3	6	5
Nausea	3	6	8	7	1
Investigations					
Weight Decreased	0	1	0	0	4
Metabolism and Nutritional Disorders					
Decreased Appetite	0	4	4	3	3
Nervous System Disorders					
Dizziness	0	6	4	6	5
Somnolence	1	0	1	2	4
Headache	6	7	5	6	0
Psychiatric Disorders					
Enuresis	0	2	4	9	9
Anxiety	1	3	1	3	1
Somnambulism	0	1	2	0	0

Dose-Response Information

In the clinical trial in adult patients with narcolepsy, a dose-response relationship was observed for enuresis and somnolence.

Additional Adverse Reactions

Adverse reactions observed in clinical studies with immediate-release sodium oxybate (≥2%), but not observed in Study 1 at a frequency of higher than 2%, and which may be relevant for LUMRYZ: diarrhea, abdominal pain upper, dry mouth, pain, feeling drunk, peripheral edema, cataplexy, muscle spasms, pain in extremity, tremor, disturbance in attention, paresthesia, sleep paralysis, disorientation, irritability, and hyperhidrosis.

Pediatric Patients (7 Years of Age and Older)

The safety of LUMRYZ for the treatment of cataplexy or excessive daytime sleepiness in pediatric patients 7 years of age and older with narcolepsy is supported by an adequate and well-controlled trial of immediate-release sodium oxybate *[see Clinical Studies (14.2)]*. Below is a display of adverse reactions of immediate-release sodium oxybate in this adequate and well-controlled trial.

In this trial, 104 patients aged 7 to 17 years (37 patients aged 7 to 11 years; 67 patients aged 12 to 17 years) with narcolepsy received immediate-release sodium oxybate for up to one year. This trial included an open-label safety continuation period in which eligible patients received immediate-release sodium oxybate for up to an additional 2 years. The median and maximum exposure across the entire trial were 371 and 987 days, respectively.

Adverse Reactions Leading to Treatment Discontinuation

In the pediatric clinical trial with immediate-release sodium oxybate, 7 of 104 patients reported adverse reactions that led to withdrawal from the study (hallucination, tactile; suicidal ideation; weight decreased; sleep apnea syndrome; affect lability; anger, anxiety, depression; and headache).

Adverse Reactions in the Pediatric Clinical Trial

The most common adverse reactions (≥5%) were nausea (20%), enuresis (19%), vomiting (18%), headache (17%), weight decreased (13%), decreased appetite (9%), dizziness (8%), and sleepwalking (6%).

Additional information regarding safety in pediatric patients appears in the following sections:

- Respiratory Depression and Sleep-Disordered Breathing *[see Warnings and Precautions (5.4)]*
- Depression and Suicidality *[see Warnings and Precautions (5.5)]*
- Other Behavioral or Psychiatric Adverse Reactions *[see Warnings and Precautions (5.6)]*
- Parasomnias *[see Warnings and Precautions (5.7)]*

The overall adverse reaction profile of immediate-release sodium oxybate in the pediatric clinical trial was similar to that seen in the adult clinical trial with immediate-release sodium oxybate. The safety profile in pediatric patients with LUMRYZ is expected to be similar to that of adult patients treated with LUMRYZ and to that of pediatric patients treated with immediate-release sodium oxybate.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of sodium oxybate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

Arthralgia, decreased appetite, fall*, fluid retention, hangover, headache, hypersensitivity, hypertension, memory impairment, nocturia, panic attack, vision blurred, and weight decreased.

*The sudden onset of sleep in patients taking sodium oxybate, including in a standing position or while rising from bed, has led to falls complicated by injuries, in some cases requiring hospitalization.

7 DRUG INTERACTIONS

7.1 Alcohol, Sedative Hypnotics, and CNS Depressants

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 *[see Warnings and Precautions (5.1)]*. In addition to coadministration of LUMRYZ and alcohol being contraindicated because of respiratory depression, consumption of alcohol while taking LUMRYZ may also result in a more rapid release of the dose of sodium oxybate *[see Clinical Pharmacology (12.3)].*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of sodium oxybate in pregnant women. Oral administration of sodium oxybate to pregnant rats (150, 350, or 1,000 mg/kg/day) or rabbits (300, 600, or 1,200 mg/kg/day) throughout organogenesis produced no clear evidence of developmental toxicity; however, oral administration to rats throughout pregnancy and lactation resulted in increased stillbirths and decreased offspring postnatal viability and growth, at a clinically relevant dose *[see Data]*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Clinical Considerations

Labor or Delivery

LUMRYZ has not been studied in labor or delivery. In obstetric anesthesia using an injectable formulation of sodium oxybate, newborns had stable cardiovascular and respiratory measures but were very sleepy, causing a slight decrease in Apgar scores. There was a fall in the rate of uterine contractions 20 minutes after injection. Placental transfer is rapid and gamma-hydroxybutyrate (GHB) has been detected in newborns at delivery after intravenous administration of GHB to mothers. Subsequent effects of sodium oxybate on later growth, development, and maturation in humans are unknown.

Data

Animal Data

Oral administration of sodium oxybate to pregnant rats (150, 350, or 1,000 mg/kg/day) or rabbits (300, 600, or 1,200 mg/kg/day) throughout organogenesis produced no clear evidence of developmental toxicity. The highest doses tested in rats and rabbits were

approximately 1 and 3 times, respectively, the maximum recommended human dose (MRHD) of 9 g per night on a body surface area (mg/m^2) basis.

Oral administration of sodium oxybate (150, 350, or 1,000 mg/kg/day) to rats throughout pregnancy and lactation resulted in increased stillbirths and decreased offspring postnatal viability and body weight gain at the highest dose tested. The no-effect dose for pre- and postnatal developmental toxicity in rats is less than the MRHD on a mg/m^2 basis.

8.2 Lactation

Risk Summary

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.

8.4 Pediatric Use

LUMRYZ has not been studied in a pediatric clinical trial. 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 *[see Adverse Reactions (6.1) and Clinical Studies (14.2)].*

In the pediatric clinical trial with immediate-release sodium oxybate administration in pediatric patients 7 years of age and older 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)].*

The safety and effectiveness of LUMRYZ have not been established in pediatric patients younger than 7 years old.

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).

8.5 Geriatric Use

Clinical studies of LUMRYZ or immediate-release sodium oxybate in patients with

narcolepsy did not include sufficient numbers of subjects age 65 years and older to determine whether they respond differently from younger subjects. In controlled trials of immediate-release sodium oxybate in another population, 39 (5%) of 874 patients were 65 years or older. Discontinuations of treatment due to adverse reactions were increased in the elderly compared to younger adults (21% vs. 19%). Frequency of headaches was markedly increased in the elderly (39% vs. 19%). The most common adverse reactions were similar in both age categories. In general, 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.

8.6 Hepatic Impairment

Because of an increase in exposure to LUMRYZ, LUMRYZ should not be initiated in patients with hepatic impairment because appropriate dosage adjustments for initiation of LUMRYZ cannot be made with the available dosage strengths *[see Clinical Pharmacology (12.3)]*. 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.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

LUMRYZ is a Schedule III controlled substance under the Federal Controlled Substances Act. Non-medical use of LUMRYZ could lead to penalties assessed under the higher Schedule I controls.

9.2 Abuse

LUMRYZ (sodium oxybate), the sodium salt of GHB, produces dose-dependent central nervous system effects, including hypnotic and positive subjective reinforcing effects. The onset of effect is rapid, enhancing its potential for abuse or misuse.

Drug abuse is the intentional non-therapeutic use of a drug product or substance, even once, for its desirable psychological or physiological effects. Misuse is the intentional use, for therapeutic purposes of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed. Drug misuse and abuse may occur with or without progression to addiction. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

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 (e.g., assault victim).

Illicit GHB is abused in social settings primarily by young adults. Some of the doses estimated to be abused are in a similar dosage range to that used for treatment of patients with cataplexy. GHB has some commonalities with ethanol over a limited dose range, and some cross tolerance with ethanol has been reported as well. Cases of

severe dependence and craving for GHB have been reported when the drug is taken around the clock. Patterns of abuse indicative of dependence include: 1) the use of increasingly large doses, 2) increased frequency of use, and 3) continued use despite adverse consequences.

Because illicit use and abuse of GHB have been reported, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of GHB (e.g., increase in size or frequency of dosing, drug-seeking behavior, feigned cataplexy). Dispose of LUMRYZ according to state and federal regulations. It is safe to dispose of LUMRYZ down the sanitary sewer.

9.3 Dependence

Dependence

Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. 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 3 to 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. In the clinical trial experience with immediate-release sodium oxybate in narcolepsy/cataplexy patients at recommended doses, two patients reported anxiety and one reported insomnia following abrupt discontinuation at the termination of the clinical trial; in the two patients with anxiety, the frequency of cataplexy had increased markedly at the same time.

Tolerance

Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose). 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. Clinical studies of immediate-release sodium oxybate in the treatment of alcohol withdrawal suggest a potential cross-tolerance with alcohol. The safety and effectiveness of LUMRYZ in the treatment of alcohol withdrawal have not been established.

10 OVERDOSAGE

10.1 Human Experience

Information regarding overdose with LUMRYZ is derived largely from reports in the medical literature that describe symptoms and signs in individuals who have ingested GHB illicitly. In these circumstances, the co-ingestion of other drugs and alcohol was

common and may have influenced the presentation and severity of clinical manifestations of overdose.

In adult clinical trials of immediate-release sodium oxybate, two cases of overdose with sodium oxybate were reported. In the first case, an estimated dose of 150 g, more than 15 times the maximum recommended dose, caused a patient to be unresponsive with brief periods of apnea and to be incontinent of urine and feces. This individual recovered without sequelae. In the second case, death was reported following a multiple drug overdose consisting of sodium oxybate and numerous other drugs.

10.2 Signs and Symptoms

Information about signs and symptoms associated with overdosage with LUMRYZ derives from reports of illicit use of GHB. Patient presentation following overdose is influenced by the dose ingested, the time since ingestion, the co-ingestion of other drugs and alcohol, and the fed or fasted state. Patients have exhibited varying degrees of depressed consciousness that may fluctuate rapidly between a confusional, agitated combative state with ataxia and coma. Emesis (even when obtunded), diaphoresis, headache, and impaired psychomotor skills have been observed. No typical pupillary changes have been described to assist in diagnosis; pupillary reactivity to light is maintained. Blurred vision has been reported. An increasing depth of coma and acidosis have been observed at higher doses. Myoclonus and tonic-clonic seizures have been reported.

Respiration may be unaffected or compromised in rate and depth. Cheyne-Stokes respiration and apnea have been observed. Bradycardia and hypothermia may accompany unconsciousness, as well as muscular hypotonia, but tendon reflexes remain intact.

10.3 Recommended Treatment of Overdose

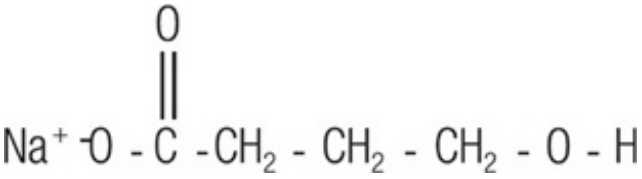
General symptomatic and supportive care should be instituted immediately, and gastric decontamination may be considered if co-ingestants are suspected. Because emesis may occur in the presence of obtundation, appropriate posture (left lateral recumbent position) and protection of the airway by intubation may be warranted. Although the gag reflex may be absent in deeply comatose patients, even unconscious patients may become combative to intubation, and rapid-sequence induction (without the use of sedative) should be considered. Vital signs and consciousness should be closely monitored. The bradycardia reported with GHB overdose has been responsive to atropine intravenous administration. No reversal of the central depressant effects of LUMRYZ can be expected from naloxone or flumazenil administration. The use of hemodialysis and other forms of extracorporeal drug removal have not been studied in GHB overdose, but have been reported in cases of acidosis associated with GHB ingestions of 125 g or greater; however, due to the rapid metabolism of sodium oxybate, these measures may not be warranted.

10.4 Poison Control Center

As with the management of all cases of drug overdosage, the possibility of multiple drug ingestion should be considered. The healthcare provider is encouraged to collect urine and blood samples for routine toxicologic screening, and to consult with a regional poison control center (1-800-222-1222) for current treatment recommendations.

11 DESCRIPTION

Sodium oxybate, a CNS depressant, is the active ingredient in LUMRYZ for extended-release oral suspension. The chemical name for sodium oxybate is sodium 4-hydroxybutyrate. The molecular formula is $C_4H_7NaO_3$, and the molecular weight is 126.09 g/mole. The chemical structure is:



Sodium oxybate is a white to off-white solid powder.

Each packet of LUMRYZ contains 4.5 g, 6 g, 7.5 g, or 9 g of sodium oxybate, equivalent to 3.7 g, 5.0 g, 6.2 g, or 7.4 g of oxybate, respectively. The inactive ingredients are carrageenan, hydrogenated vegetable oil, hydroxyethyl cellulose, magnesium stearate, malic acid, methacrylic acid copolymer, microcrystalline cellulose, povidone, and xanthan gum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

LUMRYZ is a CNS depressant. The mechanism of action of LUMRYZ in the treatment of narcolepsy is unknown. Sodium oxybate is the sodium salt of gamma-hydroxybutyrate (GHB), an endogenous compound and metabolite of the neurotransmitter GABA. It is hypothesized that the therapeutic effects of LUMRYZ on cataplexy and excessive daytime sleepiness are mediated through $GABA_B$ actions at noradrenergic and dopaminergic neurons, as well as at thalamocortical neurons.

12.3 Pharmacokinetics

Following oral administration of LUMRYZ, the plasma levels of GHB increased dose-proportionally for C_{max} and more than dose-proportionally for area under the plasma concentration-time curve (AUC_{inf}) (respectively, 2-fold and 2.3-fold increases as total daily dose is doubled from 4.5 g to 9 g).

No clinically significant difference in oxybate pharmacokinetics was observed between a single 6 g dose of LUMRYZ and two 3 g doses of immediate-release sodium oxybate administered 4 hours apart.

Absorption

Following oral administration of a single 6 g dose of LUMRYZ, the peak plasma concentration (C_{max}) was 66 mcg/mL and the time to peak plasma concentration (T_{max}) was 1.5 hours.

Effect of Food

Administration of LUMRYZ immediately after a high-fat meal resulted in a mean reduction in C_{max} and AUC of GHB by 33% and 14%, respectively; average T_{max} increased from 0.5 hours to 1.5 hours [*see Dosage and Administration (2.3)*].

Effect of Ethanol

An in vitro study showed alcohol-induced dose-dumping of sodium oxybate from extended-release oral suspension at 1 hour in the presence of 40% alcohol, and approximately 60% increase of drug release at 2 hours in the presence of 20% alcohol *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

Effect of Water Temperature

An in vitro dissolution study showed that LUMRYZ mixed with hot water (90°C) resulted in a dose-dumping phenomenon for the release of sodium oxybate, whereas warm water (50°C) did not significantly affect the drug release from the extended-release suspension [*see Dosage and Administration (2.3)].*

Effect of Water Flavoring

An in vitro dissolution study showed that LUMRYZ mixed with water prepared with calorie-free drink mix (e.g., Crystal Light Raspberry Lemonade Drink Mix) or flavored water enhancer (e.g., Mio Fruit Punch Concentrate Liquid Water Enhancer) did not impact the drug release from the extended-release suspension *[see Dosage and Administration (2.3)].*

Distribution

GHB is a hydrophilic compound with an apparent volume of distribution averaging 190 mL/kg to 384 mL/kg. At GHB concentrations ranging from 3 mcg/mL to 300 mcg/mL, less than 1% is bound to plasma proteins.

Elimination

Metabolism

Animal studies indicate that metabolism is the major elimination pathway for GHB, producing carbon dioxide and water via the tricarboxylic acid (Krebs) cycle, and secondarily by β-oxidation. The primary pathway involves a cytosolic $NADP^+$-linked enzyme, GHB dehydrogenase, which catalyzes the conversion of GHB to succinic semialdehyde, which is then biotransformed to succinic acid by the enzyme succinic semialdehyde dehydrogenase. Succinic acid enters the Krebs cycle where it is metabolized to carbon dioxide and water. A second mitochondrial oxidoreductase enzyme, a transhydrogenase, also catalyzes the conversion to succinic semialdehyde in the presence of α-ketoglutarate. An alternate pathway of biotransformation involves β-oxidation via 3,4-dihydroxybutyrate to carbon dioxide and water. No active metabolites have been identified.

Excretion

The clearance of GHB is almost entirely by biotransformation to carbon dioxide, which is then eliminated by expiration. On average, less than 5% of unchanged drug appears in human urine within 6 to 8 hours after dosing. Fecal excretion is negligible. GHB has an elimination half-life of 0.5 to 1 hour.

Specific Population

Geriatric Patients

There is limited experience with LUMRYZ in the elderly. Results from a pharmacokinetic study of immediate-release sodium oxybate (n=20) in another studied population

indicate that the pharmacokinetic characteristics of GHB are consistent among younger (age 48 to 64 years) and older (age 65 to 75 years) adults.

Pediatric Patients

The pharmacokinetics of LUMRYZ has not been directly evaluated in pediatric patients.

The pharmacokinetics of immediate-release sodium oxybate were evaluated in pediatric patients 7 to 17 years of age (n=29). The pharmacokinetic characteristics of immediate-release sodium oxybate were shown to be similar in adults and pediatric patients. Body weight was found to be the major intrinsic factor affecting oxybate pharmacokinetics.

Male and Female Patients

In a study of 18 female and 18 male healthy adult volunteers, no gender differences were detected in the pharmacokinetics of GHB following an immediate-release 4.5 g oral dose of sodium oxybate.

Racial or Ethnic Groups

There are insufficient data to evaluate any pharmacokinetic differences among races.

Patients with Renal Impairment

No pharmacokinetic study in patients with renal impairment has been conducted.

Patients with Hepatic Impairment

The pharmacokinetics of GHB in 16 cirrhotic patients, half without ascites (Child's Class A) and half with ascites (Child's Class C), were compared to the kinetics in 8 subjects with normal hepatic function, after a single sodium oxybate oral dose of 25 mg/kg. AUC values were doubled in cirrhotic patients, with apparent oral clearance reduced from 9.1 mL/min/kg in healthy adults to 4.5 and 4.1 mL/min/kg in Class A and Class C patients, respectively. Elimination half-life was significantly longer in Class C and Class A patients than in control patients (mean $t_{1/2}$ of 59 minutes and 32 minutes, respectively, versus 22 minutes in control patients). LUMRYZ should not be initiated in patients with liver impairment *[see Use in Specific Populations (8.6)].*

Drug Interaction Studies

In vitro studies with pooled human liver microsomes indicate that sodium oxybate does not significantly inhibit the activities of the human isoenzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A, up to the concentration of 3 mM (378 mcg/mL), a level considerably higher than levels achieved with the maximum recommended dose.

A drug interaction study in healthy adults (age 18 to 55 years) was conducted with LUMRYZ and divalproex sodium. Co-administration of a single dose of LUMRYZ (6 g) with divalproex sodium ER at steady state resulted in an approximate 18% increase in AUC (90% CI ratio range of 112%-123%), which is not expected to be clinically meaningful, while C_{max} was comparable. A single dose of LUMRYZ (6 g) did not appear to affect the pharmacokinetics of divalproex sodium. However, a pharmacodynamic interaction between LUMRYZ and divalproex sodium, a sedative antiepileptic drug, cannot be ruled out *[see Warnings and Precautions (5.1) and Drug Interactions (7.1)]*.

Drug interaction studies in healthy adults (age 18 to 50 years) were conducted with immediate-release sodium oxybate and diclofenac and ibuprofen:

- Diclofenac: Co-administration of sodium oxybate (6 g per day as two equal

doses of 3 grams dosed four hours apart) with diclofenac (50 mg/dose twice per day) showed no significant changes in systemic exposure to GHB. Co-administration did not appear to affect the pharmacokinetics of diclofenac.

- Ibuprofen: Co-administration of sodium oxybate (6 g per day as two equal doses of 3 grams dosed four hours apart) with ibuprofen (800 mg/dose four times per day also dosed four hours apart) resulted in comparable systemic exposure to GHB, as shown by plasma C_{max} and AUC values. Co-administration did not affect the pharmacokinetics of ibuprofen.

Drug interaction studies in healthy adults demonstrated no pharmacokinetic interactions between immediate-release sodium oxybate and protriptyline hydrochloride, zolpidem tartrate, and modafinil. Also, there were no pharmacokinetic interactions with the alcohol dehydrogenase inhibitor fomepizole. However, pharmacodynamic interactions with these drugs cannot be ruled out. Alteration of gastric pH with omeprazole produced no significant change in the pharmacokinetics of GHB. In addition, drug interaction studies in healthy adults demonstrated no pharmacokinetic or clinically significant pharmacodynamic interactions between immediate-release sodium oxybate and duloxetine HCl.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Administration of sodium oxybate to rats at oral doses of up to 1,000 mg/kg/day for 83 (males) or 104 (females) weeks resulted in no increase in tumors. Plasma exposure (AUC) at the highest dose tested was 2 times that in humans at the maximum recommended human dose (MRHD) of 9 g per night.

The results of 2-year carcinogenicity studies in mouse and rat with gamma-butyrolactone, a compound that is metabolized to sodium oxybate *in vivo,* showed no clear evidence of carcinogenic activity. The plasma AUCs of sodium oxybate achieved at the highest doses tested in these studies were less than that in humans at the MRHD.

Mutagenesis

Sodium oxybate was negative in the *in vitro* bacterial gene mutation assay, an *in vitro* chromosomal aberration assay in mammalian cells, and in an *in vivo* rat micronucleus assay.

Impairment of Fertility

Oral administration of sodium oxybate (150, 350, or 1,000 mg/kg/day) to male and female rats prior to and throughout mating and continuing in females through early gestation resulted in no adverse effects on fertility. The highest dose tested is approximately equal to the MRHD on a mg/m^2 basis.

14 CLINICAL STUDIES

14.1 Cataplexy and Excessive Daytime Sleepiness (EDS) in Adult Narcolepsy

The effectiveness of LUMRYZ for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy has been established based on a double-blind, randomized, placebo-controlled, two-arm multi-center study to assess the efficacy and safety of a once nightly administration of LUMRYZ in patients with narcolepsy (Study 1; NCT02720744).

A total of 212 patients were randomized to receive LUMRYZ or placebo in a 1:1 ratio and received at least one dose of study drug. The study was divided into four sequential study periods, and incorporated dose titration to stabilized dose administration of LUMRYZ (4.5 g, 6 g, 7.5 g, and 9 g). There was a three-week screening period, a 13-week treatment period including up-titration over a period of eight weeks, five weeks of stable dosing at 9 g/night, and a one-week follow-up period. Patients could be on concomitant stimulant as long as dosage was stable for 3 weeks prior to study start.

The three co-primary endpoints were the Maintenance of Wakefulness Test (MWT), Clinical Global Impression-Improvement (CGI-I), and mean change in weekly cataplexy attacks. The MWT measures latency to sleep onset (in minutes), averaged over five sessions at 2-hour intervals following nocturnal polysomnography. For each test session, patients were instructed to remain awake for as long as possible during 30-minute test sessions, and sleep latency was determined as the number of minutes patients could remain awake. The overall score was the mean sleep latency for the 5 sessions. The CGI-I was evaluated on a 7-point scale, centered at *No Change,* and ranging from *Very Much Worse* to *Very Much Improved*. Patients were rated by evaluators who based their assessments on the severity of narcolepsy at Baseline.

Demographic and mean baseline characteristics were similar for the LUMRYZ and placebo groups. A total of 76% were narcolepsy type 1 (NT1; with both symptoms of EDS and cataplexy) patients, and 24% were narcolepsy type 2 (NT2; with symptoms of EDS and without cataplexy) patients. The mean age was 31 years, and 68% were female. Approximately 63% of patients were on concomitant stimulant use. The mean MWT at baseline was 5 minutes for the LUMRYZ group, and 4.7 minutes for the placebo group. The mean number of cataplexy attacks per week at baseline was 18.9 in the LUMRYZ group and 19.8 in the placebo group. A statistically significant improvement was seen on the MWT, CGI-I, and mean weekly cataplexy attacks, for the 6 g (Week 3), 7.5 g (Week 8), and 9 g (Week 13) dose of LUMRYZ, compared to the placebo group (see Table 3, Table 4, and Table 5).

Table 3: Change from Baseline in the Maintenance of Wakefulness Test

Dose	**Treatment Group (N)**	**Change from Baseline (Minutes)***	**Difference from Placebo [95% CI]**	**p-value**
6 g (Week 3)	LUMRYZ (87)	8.1	5.0 [2.90;7.05]	<0.001
	Placebo (88)	3.1	-	-
7.5 g (Week 8)	LUMRYZ (76)	9.6	6.2 [3.84;8.58]	<0.001
	Placebo (78)	3.3	-	-
9 g (Week 13)	LUMRYZ (68)	10.8	6.1 [3.52;8.75]	<0.001
	Placebo (78)	4.7	-	-

*Mean MWT at baseline was 5.0 minutes for the LUMRYZ group and 4.7 minutes for the placebo group

Table 4: Proportion of Patients with a Very Much or Much Improved Clinical Global Impression-Improvement

Dose	Treatment Group (N)	Percentage of Responders (Much or Very Much Improved)	Odds Ratio [95% CI]	p-value
6 g (Week 3)	LUMRYZ (87)	40	10.3 [3.93;26.92]	<0.001
	Placebo (87)	6	-	-
7.5 g (Week 8)	LUMRYZ (75)	64	5.7 [2.82;11.40]	<0.001
	Placebo (81)	22	-	-
9 g (Week 13)	LUMRYZ (69)	73	5.6 [2.76;11.23]	<0.001
	Placebo (79)	32	-	-

Table 5: Change from Baseline in the Mean Cataplexy Attacks Per Week in NT1 Patients

Dose	Treatment Group (N)	Change from Baseline*	Difference from Placebo [95% CI]	p-value
6 g (Week 3)	LUMRYZ (73)	-7.4	-4.8 [-7.03;-2.62]	<0.001
	Placebo (72)	-2.6	-	-
7.5 g (Week 8)	LUMRYZ (66)	-10.0	-6.3 [-8.74;-3.80]	<0.001
	Placebo (69)	-3.7	-	-
9 g (Week 13)	LUMRYZ (55)	-11.5	-6.7 [-9.32;-3.98]	<0.001
	Placebo (62)	-4.9	-	-

*Mean (SD) number of cataplexy attacks per week at baseline was 18.9 (8.7) in the LUMRYZ group and 19.8 (8.9) in the placebo group

14.2 Cataplexy and Excessive Daytime Sleepiness (EDS) in Pediatric Narcolepsy

The effectiveness of LUMRYZ in pediatric patients is based upon a clinical study in patients treated with immediate-release sodium oxybate, as described below.

The effectiveness of immediate-release sodium oxybate in the treatment of cataplexy or excessive daytime sleepiness in pediatric patients 7 years of age and older with narcolepsy was established in a double-blind, placebo-controlled, randomized-withdrawal study (NCT02221869). The study was conducted in 106 pediatric patients (median age: 12 years; range: 7 to 17 years) with a baseline history of at least 14 cataplexy attacks in a typical 2-week period prior to any treatment for narcolepsy symptoms. Of the 106 patients, 2 did not receive study drug and 63 patients were randomized 1:1 either to continued treatment with immediate-release sodium oxybate or to placebo. Randomization to placebo was stopped early as the efficacy criterion was met at the pre-planned interim analysis.

Patients entered the study either taking a stable dosage of immediate-release sodium oxybate or were immediate-release sodium oxybate-naïve. CNS stimulants were allowed at entry, and approximately 50% of patients continued taking a stable dose of stimulant throughout the stable-dose and double-blind periods. Immediate-release sodium

oxybate-naïve patients were initiated and titrated based on body weight over a period of up to 10 weeks. The total nightly dose was administered in two divided doses, with the first dose given at nighttime and the second given 2.5 to 4 hours later. Once a stable dosage of immediate-release sodium oxybate had been achieved, these patients entered the 2-week stable-dose period; patients on a stable dosage of immediate-release sodium oxybate at study entry remained on this dosage for 3 weeks prior to randomization. Efficacy was established at dosages ranging from 3 g to 9 g of immediate-release sodium oxybate per night.

The primary efficacy measure was the change in frequency of cataplexy attacks. In addition, change in cataplexy severity was evaluated with the Clinical Global Impression of Change for cataplexy severity. The Clinical Global Impression of Change is evaluated on a 7-point scale, centered at No Change, and ranging from Very Much Worse to Very Much Improved. The efficacy of immediate-release sodium oxybate in the treatment of excessive daytime sleepiness in pediatric patients with narcolepsy was evaluated with the change in the Epworth Sleepiness Scale (Child and Adolescent) score. The Epworth Sleepiness Scale (Child and Adolescent) is a modified version of the Epworth Sleepiness Scale used in the adult clinical trial with immediate-release sodium oxybate. The Epworth Sleepiness Scale is intended to evaluate the extent of sleepiness in everyday situations by asking the patient a series of questions. In these questions, patients were asked to rate their chances of dozing during each of 8 activities on a scale from 0-3 (0=never; 1=slight; 2=moderate; 3=high). Higher total scores indicate a greater tendency to sleepiness. The overall change in narcolepsy condition was assessed by the Clinical Global Impression of Change for narcolepsy overall. Efficacy was assessed during or at the end of the 2-week double-blind treatment period, relative to the last 2 weeks or end of the stable-dose period (see Tables 6 and 7).

Pediatric patients taking stable dosages of immediate-release sodium oxybate who were withdrawn from immediate-release sodium oxybate treatment and were randomized to placebo during the double-blind treatment period experienced a statistically significant increase in weekly cataplexy attacks compared with patients who were randomized to continue treatment with immediate-release sodium oxybate. Patients randomized to receive placebo during the double-blind treatment period experienced a statistically significant worsening of EDS compared with patients randomized to continue receiving immediate-release sodium oxybate (see Table 6).

Table 6: Number of Weekly Cataplexy Attacks and Epworth Sleepiness Scale (Child and Adolescent) Score

Treatment Group	**Baseline[*,†]**	**Double-blind Treatment Period[‡,§]**	**Median Change from Baseline**	**Comparison to Placebo (p-value[¶])**
Median Number of Cataplexy Attacks (attacks/week)				
Placebo (n=32)	4.7	21.3	12.7	-
Immediate-release Sodium Oxybate (n=31)	3.5	3.8	0.3	<0.0001
Median Epworth Sleepiness Scale (Child and Adolescent) Score				
Placebo (n=31[**])	11	12	3	-

Immediate-release Sodium Oxybate (n=30**)	8	9	0	0.0004

* For weekly number of cataplexy attacks, baseline value is calculated from the last 14 days of the stable-dose period.
† For Epworth Sleepiness Scale score, baseline value is collected at the end of stable-dose period.
‡ Weekly number of cataplexy attacks is calculated from all days within the double-blind treatment period.
§ For Epworth Sleepiness Scale, value is collected at the end of the double-blind treatment period.
¶ P-value from rank-based analysis of covariance (ANCOVA) with treatment as a factor and rank baseline value as a covariate.
** One patient in each of the treatment groups did not have baseline ESS score available and were not included in this analysis.

Patients randomized to receive placebo during the double-blind treatment period experienced a statistically significant worsening of cataplexy severity and narcolepsy overall according to the clinician's assessment compared with patients randomized to continue receiving immediate-release sodium oxybate (see Table 7).

Table 7: Clinical Global Impression of Change (CGIc) for Cataplexy Severity and Narcolepsy Overall

Worsened, %†	**CGIc Cataplexy Severity***		**CGIc Narcolepsy Overall***	
	Placebo (n=32)	Immediate-release Sodium Oxybate (n=29)‡	Placebo (n=32)	Immediate-release Sodium Oxybate (n=29)‡
Much worse or very much worse	66%	17%	59%	10%
p-value§	0.0001		<0.0001	

* Responses indicate change of severity or symptoms relative to receiving immediate-release sodium oxybate treatment at baseline.
† Percentages based on total number of observed values.
‡ Two patients randomized to immediate-release sodium oxybate did not have the CGIc assessments completed and were excluded from the analysis.
§ P-value from Pearson's chi-square test.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

LUMRYZ is a blend of white to off-white granules for extended-release oral suspension in water. LUMRYZ is supplied in cartons and a 28-day starter pack.

Cartons: each carton contains either 7 or 30 packets of LUMRYZ, a mixing cup, Prescribing Information and Medication Guide, and Instructions for Use (see Table 8). Dose packets contain a single dose of LUMRYZ provided in 4.5 g, 6 g, 7.5 g, or 9 g

doses.

Table 8: LUMRYZ Carton Configurations

Strength	Package Size	NDC Number
4.5 g	7 packets	NDC 13551-001-07
	30 packets	NDC 13551-001-30
6 g	7 packets	NDC 13551-002-07
	30 packets	NDC 13551-002-30
7.5 g	7 packets	NDC 13551-003-07
	30 packets	NDC 13551-003-30
9 g	7 packets	NDC 13551-004-07
	30 packets	NDC 13551-004-30

28-day Starter Pack: contains four 7-count cartons, each containing a mixing cup, Prescribing Information and Medication Guide, and Instructions for Use (see Table 9). Dose packets contain a single dose of LUMRYZ provided in 4.5 g, 6 g, or 7.5 g doses.

Table 9: LUMRYZ Starter Pack Contents

28-day Starter Pack	Strength	Package Size	NDC Number
Week 1	4.5 g	7 packets	NDC 13551-005-01
Week 2	6 g	7 packets	
Week 3	6 g	7 packets	
Week 4	7.5 g	7 packets	

16.2 Storage

Keep out of reach of children.

LUMRYZ should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP Controlled Room Temperature).

Suspensions should be consumed within 30 minutes.

16.3 Handling and Disposal

LUMRYZ is a Schedule III drug under the Controlled Substances Act. LUMRYZ should be handled according to state and federal regulations. It is safe to dispose of LUMRYZ down the sanitary sewer.

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Central Nervous System Depression

Inform patients and/or caregivers that LUMRYZ can cause central nervous system depression, including respiratory depression, hypotension, profound sedation, syncope, and death. Instruct patients to not engage in activities requiring mental alertness or motor coordination, including operating hazardous machinery, for at least 6 hours after taking LUMRYZ. Instruct patients and/or caregivers to inform their healthcare providers of all the medications they take *[see Warnings and Precautions (5.1)].*

Abuse and Misuse

Inform patients and/or caregivers that the active ingredient of LUMRYZ is gamma-hydroxybutyrate (GHB), which is associated with serious adverse reactions with illicit use and abuse *[see Warnings and Precautions (5.2)].*

LUMRYZ REMS

LUMRYZ is available only through a restricted program called the LUMRYZ REMS *[see Warnings and Precautions (5.3)]*. Inform the patient and/or caregiver of the following notable requirements:

- LUMRYZ is dispensed only by pharmacies that are specially certified
- LUMRYZ will be dispensed and shipped only to patients who are enrolled in the LUMRYZ REMS

LUMRYZ is available only from certified pharmacies participating in the program. Therefore, provide patients and/or caregivers with the telephone number and website for information on how to obtain the product.

Alcohol or Sedative Hypnotics

Advise patients and/or caregivers that alcohol and other sedative hypnotics should not be taken with LUMRYZ *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

Sedation

Inform patients and/or caregivers that they are likely to fall asleep quickly after taking LUMRYZ (often within 5 and usually within 15 minutes), but the time it takes to fall asleep can vary from night to night. The sudden onset of sleep, including in a standing position or while rising from bed, has led to falls complicated by injuries, in some cases requiring hospitalization *[see Adverse Reactions (6.2)]*. Instruct patients and/or caregivers that they should remain in bed following ingestion of their dose *[see Dosage and Administration (2.3)]*.

Food Effects on LUMRYZ

Inform patients and/or caregivers that LUMRYZ should be taken at least 2 hours after eating.

Respiratory Depression and Sleep-Disordered Breathing

Inform patients and/or caregivers that LUMRYZ may impair respiratory drive, especially in patients with compromised respiratory function, and may cause apnea *[see Warnings and Precautions (5.4)].*

Depression and Suicidality

Instruct patients and/or caregivers to contact a healthcare provider immediately if they develop depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or suicidal ideation *[see Warnings and Precautions (5.5)].*

Other Behavioral or Psychiatric Adverse Reactions

Inform patients and/or caregivers that LUMRYZ can cause behavioral or psychiatric adverse reactions, including confusion, anxiety, and psychosis. Instruct them to notify their healthcare provider if any of these types of symptoms occur *[see Warnings and Precautions (5.6)].*

Sleepwalking

Instruct patients and/or caregivers that LUMRYZ has been associated with sleepwalking and other behaviors during sleep, and to contact their healthcare provider if this occurs *[see Warnings and Precautions (5.7)].*

Sodium Intake

Instruct patients and/or caregivers that LUMRYZ contains a significant amount of sodium and patients who are sensitive to sodium intake (e.g., those with heart failure, hypertension, or renal impairment) should limit their sodium intake *[see Warnings and Precautions (5.8)].*

Manufactured for:

Alkermes, Inc.
Waltham, MA 02451

Protected by U.S. Patent No. D1,032,378

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LUM-PI:R4

Medication Guide
LUMRYZ® (LOOM rize)
(sodium oxybate)
for extended-release oral suspension, CIII

Read this Medication Guide carefully before you start taking LUMRYZ and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or treatment.

What is the most important information I should know about LUMRYZ?

- LUMRYZ is a central nervous system (CNS) depressant. Taking LUMRYZ with other CNS depressants such as medicines used to make you fall asleep, including opioid analgesics, benzodiazepines, sedating antidepressants, antipsychotics, sedating anti-epileptic medicines, general anesthetics, muscle relaxants, alcohol, or street drugs, may cause serious medical problems, including:
  - trouble breathing (respiratory depression)
  - low blood pressure (hypotension)
  - changes in alertness (drowsiness)
  - fainting (syncope)
  - death

  Ask your doctor if you are not sure if you are taking a medicine listed above.
- LUMRYZ is a federal controlled substance (CIII). The active ingredient of LUMRYZ is a form of gamma-hydroxybutyrate (GHB) that is also a federal controlled substance (CI). Abuse of illegal GHB, either alone or with other CNS depressants may cause serious medical problems, including:
  - seizure
  - trouble breathing (respiratory depression)
  - changes in alertness (drowsiness)
  - coma
  - death

  Call your doctor right away if you have any of these serious side effects.
- Anyone who takes LUMRYZ should not do anything that requires them to be fully awake or is dangerous, including driving a car, using heavy machinery, or flying an airplane, for at least 6 hours after taking LUMRYZ. Those activities should not be done until you know how LUMRYZ affects you.
- Keep LUMRYZ in a safe place to prevent abuse and misuse. Selling or giving away LUMRYZ may harm others and is against the law. Tell your doctor if you have ever abused or been dependent on alcohol, prescription medicines, or street drugs.
- Because of the risk of CNS depression, abuse, and misuse, LUMRYZ is available only by prescription and filled through certified pharmacies in the LUMRYZ REMS. You must be enrolled in the LUMRYZ REMS to receive LUMRYZ. For more information on how to receive LUMRYZ, visit www.LUMRYZREMS.com. Before you receive LUMRYZ, your doctor or pharmacist will make sure that you understand how to use LUMRYZ safely and effectively. If you have any questions about LUMRYZ, ask your doctor or call the LUMRYZ REMS at 1-877-453-1029.

What is LUMRYZ?

LUMRYZ is a prescription medicine used in people 7 years of age or older to treat the following symptoms of narcolepsy:

- sudden onset of weak or paralyzed muscles (cataplexy), or
- excessive daytime sleepiness (EDS)

It is not known if LUMRYZ is safe and effective in children under 7 years of age.

Do not take LUMRYZ if you or your child:

- take other sleep medicines or sedatives (medicines that cause sleepiness)
- drink alcohol
- have a rare problem called succinic semialdehyde dehydrogenase deficiency

Before taking LUMRYZ, tell your doctor about all medical conditions, including if you or your child:

- have a history of drug abuse.
- have short periods of not breathing while sleeping (sleep apnea).
- have trouble breathing or have lung problems. You or your child may have a higher chance of having serious breathing problems when taking LUMRYZ.
- have or had depression or have tried to harm yourself. You or your child should be watched carefully for new symptoms of depression.
- have or had behavior or other psychiatric problems such as:
  - anxiety
  - seeing or hearing things that are not real (hallucinations)
  - feeling more suspicious (paranoia)
  - being out of touch with reality (psychosis)
  - acting aggressive
  - agitation
- have liver problems.
- are on a salt-restricted diet. LUMRYZ contains a lot of sodium (salt) and may not be right for you or your child.
- have high blood pressure.
- have heart failure.
- have kidney problems.
- are pregnant or plan to become pregnant. It is not known if LUMRYZ can harm your unborn baby.
- are breastfeeding or plan to breastfeed. LUMRYZ passes into breast milk. You and your doctor should decide if you or your child will take LUMRYZ or breastfeed.

Tell your doctor about all the medicines you or your child take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Especially, tell your doctor if you or your child take other medicines to help you or your child sleep (sedatives) or that may make you or your child sleepy, such as some medicines to treat pain, anxiety, depression, or seizures. Know the medicines you or your child takes. Keep a list of them to show your doctor and pharmacist when you or your child get a new medicine.

How should I take or give LUMRYZ?

- Read the **Instructions for Use** for detailed instructions on how to

take or give LUMRYZ.

- Take or give LUMRYZ exactly as your doctor tells you to take or give it.
- LUMRYZ is taken by mouth 1 time at bedtime.
- Wait at least 2 hours after eating before taking or giving LUMRYZ.
- After mixing LUMRYZ, take or give it within 30 minutes. Do not mix LUMRYZ with hot water.
- Take or give LUMRYZ at bedtime while you or your child is in bed and lie down immediately. You or your child should remain in bed after taking LUMRYZ.
- LUMRYZ can cause physical dependence and craving for the medicine when it is not taken as directed.
- Never change the LUMRYZ dose without talking to your or your child's doctor.
- LUMRYZ can cause sleep very quickly without feeling drowsy. Some people fall asleep within 5 minutes and most fall asleep within 15 minutes. The time it takes to fall asleep might be different from night to night.
- Falling asleep quickly, including while standing or while getting up from the bed, has led to falls with injuries that have required some people to be hospitalized.
- If you or your child take too much LUMRYZ, call your doctor or go to the nearest hospital emergency room right away.

What are the possible side effects of LUMRYZ?

LUMRYZ can cause serious side effects, including:

- See **"What is the most important information I should know about LUMRYZ?"**
- **breathing problems, including:**
  - slower breathing.
  - trouble breathing.
  - short periods of not breathing while sleeping (sleep apnea).

People who already have breathing or lung problems have a higher chance of having breathing problems when they use LUMRYZ.

- **mental health problems, including:**
  - confusion
  - seeing or hearing things that are not real (hallucinations)
  - unusual or disturbing thoughts (abnormal thinking)
  - feeling anxious or upset
  - depression
  - thoughts of killing yourself or trying to kill yourself
  - increased tiredness
  - feelings of guilt or worthlessness
  - difficulty concentrating

Call your doctor right away if you or your child has symptoms of mental health problems, or a change in weight or appetite.

- **sleepwalking.** Sleepwalking can cause injuries. Call your doctor if you start or your child starts sleepwalking. Your doctor should check you or your child.

The most common side effects of LUMRYZ in adults include:

- nausea
- dizziness
- bedwetting

- headache
- vomiting

The most common side effects of LUMRYZ in children 7 years of age and older include:

- nausea
- bedwetting
- vomiting
- headache
- decreased weight
- decreased appetite
- dizziness
- sleepwalking

Side effects may increase when taking higher doses of LUMRYZ.
These are not all the possible side effects of LUMRYZ. For more information, ask your doctor or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store LUMRYZ?

- Store LUMRYZ at room temperature between 68°F to 77°F (20°C to 25°C).
- Store LUMRYZ in the original packet prior to mixing with water.
- LUMRYZ suspension should be taken within 30 minutes of preparation.
- When you have finished using the LUMRYZ packet, throw it away (dispose of it) in the trash. If any LUMRYZ remains in the packet, rinse it down the sink before throwing away.

Keep LUMRYZ and all medicines out of the reach of children and pets.

General information about the safe and effective use of LUMRYZ.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use LUMRYZ for a condition for which it was not prescribed. Do not give LUMRYZ to other people, even if they have the same symptoms. It may harm them.
You can ask your pharmacist or doctor for information about LUMRYZ that is written for health professionals.

What are the ingredients in LUMRYZ?
Active ingredients: sodium oxybate
Inactive ingredients: carrageenan, hydrogenated vegetable oil, hydroxyethyl cellulose, magnesium stearate, malic acid, methacrylic acid copolymer, microcrystalline cellulose, povidone, xanthan gum.
Manufactured For:
Alkermes, Inc. Waltham, MA 02451
For more information, go to www.LUMRYZREMS.com or call the LUMRYZ REMS at 1-877-453-1029.
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This Medication Guide has been approved by the U.S. Food and Drug Administration.
Revised: 08/2026
LUM-MG:R4

INSTRUCTIONS FOR USE

INSTRUCTIONS FOR USE

Lumryz (sodium oxybate) for extended-release oral suspension ℂ 1 packet per dose

Alkermes

This Instructions for Use contains information on how to take LUMRYZ. Read this Instructions for Use before you (or your child) take LUMRYZ and each time you (or your child) get a refill. There may be new information.

This information does not take the place of talking to your doctor about your (or your child's) medical condition or your (or your child's) treatment. **If you have questions, please talk with your doctor.**

Important information when taking LUMRYZ

● Take (or give) 1 packet of LUMRYZ each day at bedtime.

● You will need to mix LUMRYZ with water before you take or give your child the dose.

● You (or your child) should avoid getting out of bed after taking LUMRYZ. Some people fall asleep within 5 minutes of taking LUMRYZ and most will fall asleep within 15 minutes. The time it takes to fall asleep might be different from night to night.

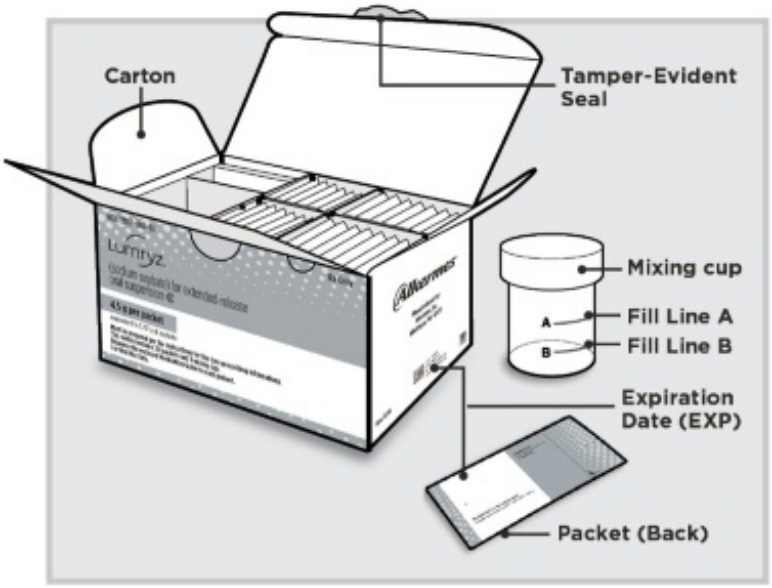
● Medicines that cause sleepiness should not be used while taking LUMRYZ.

● **Do not** use LUMRYZ with alcohol.

● **Do not** drive or operate heavy machinery within 6 hours of taking LUMRYZ. Those activities should not be done until you know how LUMRYZ affects you.

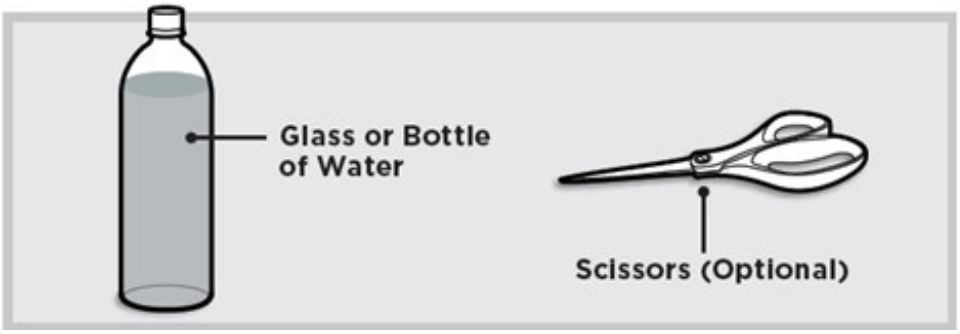
● Mix and take (or give) LUMRYZ within 30 minutes. If not taken or given within 30 minutes of mixing, throw it away (dispose of it) and prepare a new dose.

LUMRYZ carton and contents



LUMRYZ comes in different package sizes. The LUMRYZ package you receive may look different from the picture shown above.

Additional supplies needed



How should I store LUMRYZ?

- Store LUMRYZ at room temperature, between 68°F to 77°F (20°C to 25°C).
- Store LUMRYZ in the original packet prior to mixing with water.
- LUMRYZ suspension should be taken within 30 minutes of preparation.
- When you have finished using the LUMRYZ packet, throw it away (dispose of it) in the trash. If any LUMRYZ remains in the packet, rinse it down the sink before throwing away.
- Store LUMRYZ and all medicines out of the reach of children and pets.

Before using LUMRYZ

- Before using a new LUMRYZ carton, check the tamper-evident seal on the carton lid to make sure it is not missing or broken.

● **Do not** use if the tamper-evident seal is missing or broken.

● Check the expiration date (EXP) on the LUMRYZ carton.

● **Do not** use LUMRYZ after the expiration date (EXP) on the label has passed.

● Open the LUMRYZ carton by tearing the tamper-evident seal with your hands or by using a pair of scissors.

Before each use

● Clean the mixing cup by rinsing it with water and letting it dry before each use.

● **Do not** use a measuring device other than the mixing cup that comes in your LUMRYZ carton to measure and take a dose of LUMRYZ.

● Check the expiration date (EXP) on the packet label. **Do not** use the LUMRYZ packet after the expiration date (EXP) has passed.

Important: Make sure to prepare LUMRYZ at bedside.

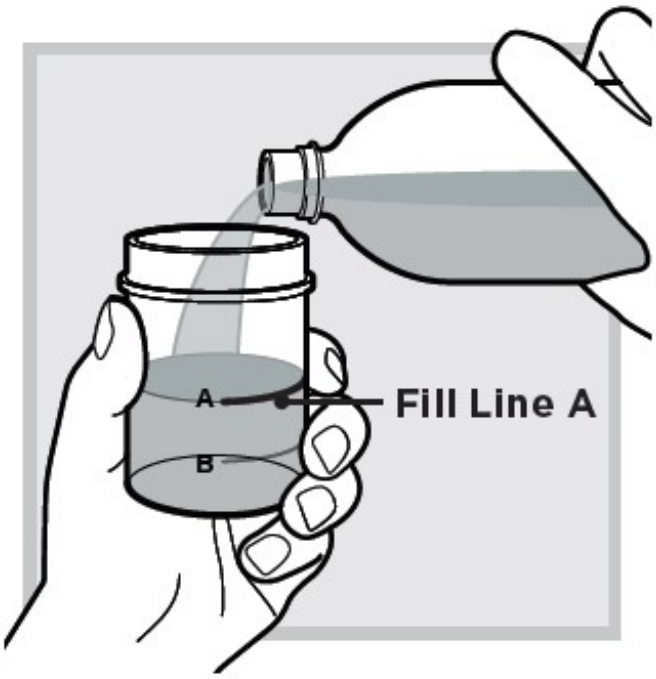
Gather the following supplies and place them on a flat surface at your (or your child's) bedside:

- 1 bottle or glass of water (1/3 cup). Do not use hot water. Water may be mixed with calorie-free drink mix or flavored water enhancer.
- 1 LUMRYZ packet
- 1 clean mixing cup. The cap is not child resistant.
- 1 pair of scissors (optional)

Mix the LUMRYZ solution at your (or your child's) bedside

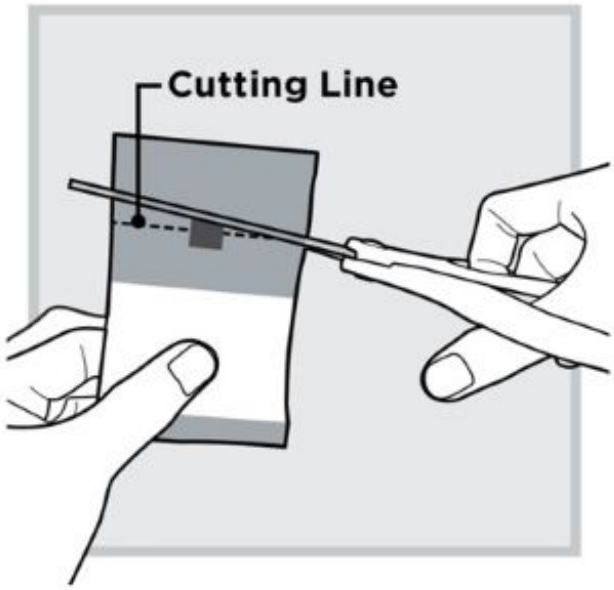
1.) At your (or your child's) bedside, open the mixing cup by twisting the cap to the left (counter-clockwise) to remove it.

2.) Fill the mixing cup with water up to **Fill Line A** (top line) and set the mixing cup down on a flat surface.

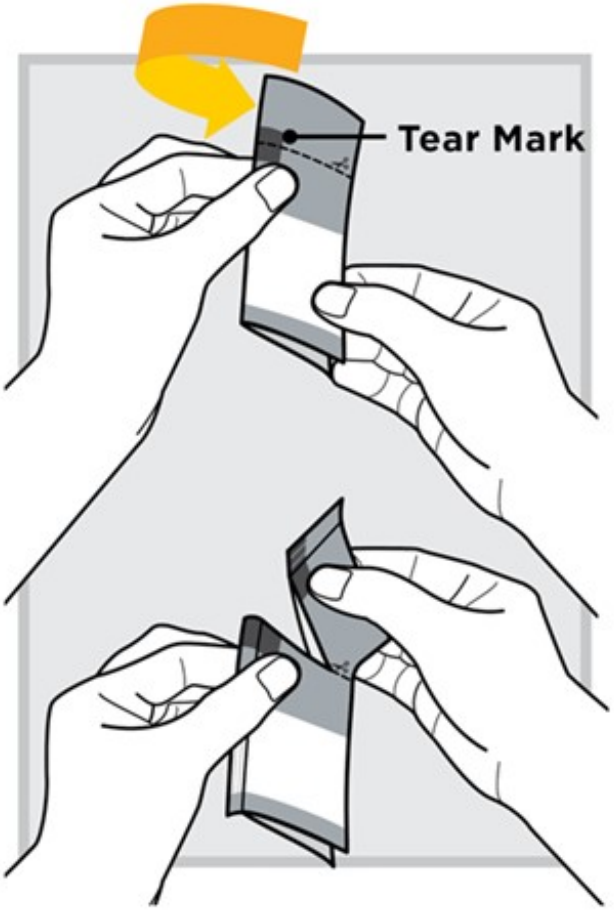


3.) Open 1 packet:

Use scissors to cut open the packet along the **Cutting Line**, located on the back of the packet.



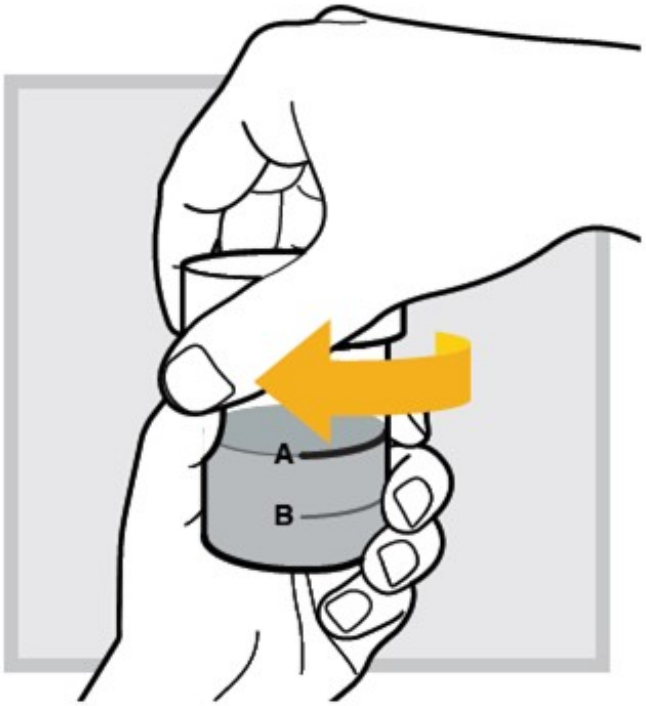
Fold the packet in half at the gray **Tear Mark** located on the back of the packet. Tear the packet open with your hands.



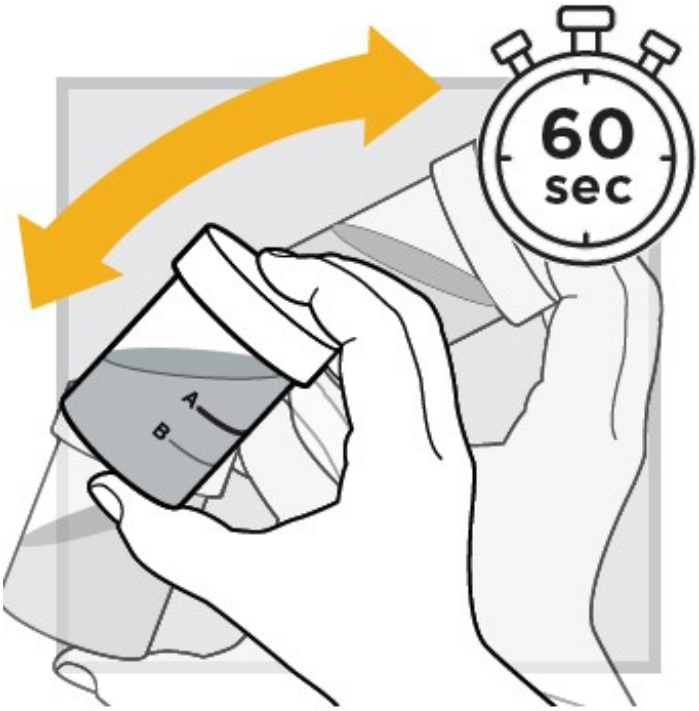
4.) Pour the entire content from the packet into the water-filled mixing cup.

Make sure there is no powder left in the packet.

5.) Close the mixing cup by twisting the cap to the right (clockwise) until firmly closed.



6.) Mix the water and powder solution by shaking the closed mixing cup well for at least **60 seconds (1 minute)**.



7.) Make sure the solution is mixed thoroughly.

The mixed solution will appear slightly milky with some lumps.

The mixing cup cap is not child resistant. If the mixed solution is not drank immediately, then do not remove the cap, and keep out of reach of children.

Take the LUMRYZ solution at your (or your child's) bedside

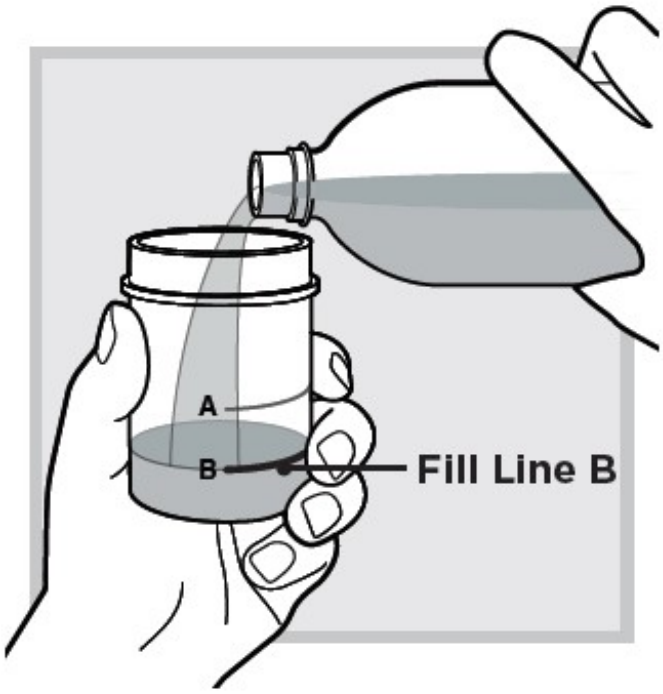
8.) Open the mixing cup by twisting the cap to the left (counter-clockwise) and remove it.

9.) While sitting in bed drink (or have your child drink) the mixed solution within **30 minutes** of mixing.

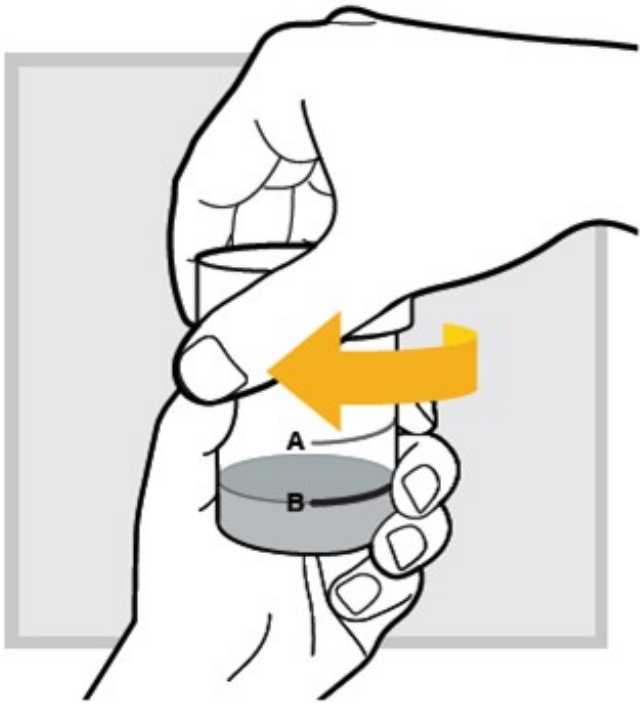
Make sure you (or your child) drink all the mixed solution in the mixing cup.

10.) Immediately refill the mixing cup with water up to **Fill Line B** (lower line) to mix in any medicine left in the mixing cup.

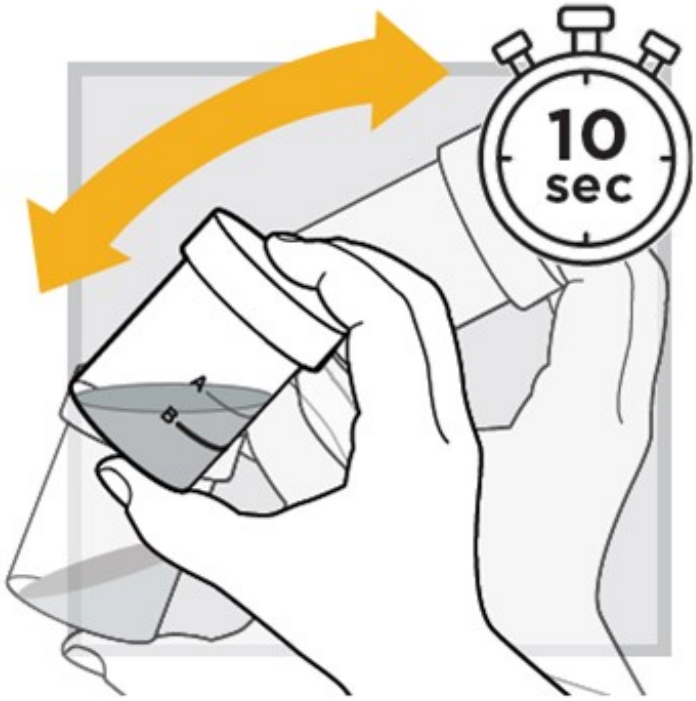
Do not open another packet of LUMRYZ. Take (or give) only 1 packet each day at bedtime.



11.) Close the mixing cup by twisting the cap to the right (clockwise) until firmly closed.



12.) Shake well again for **10 seconds**.



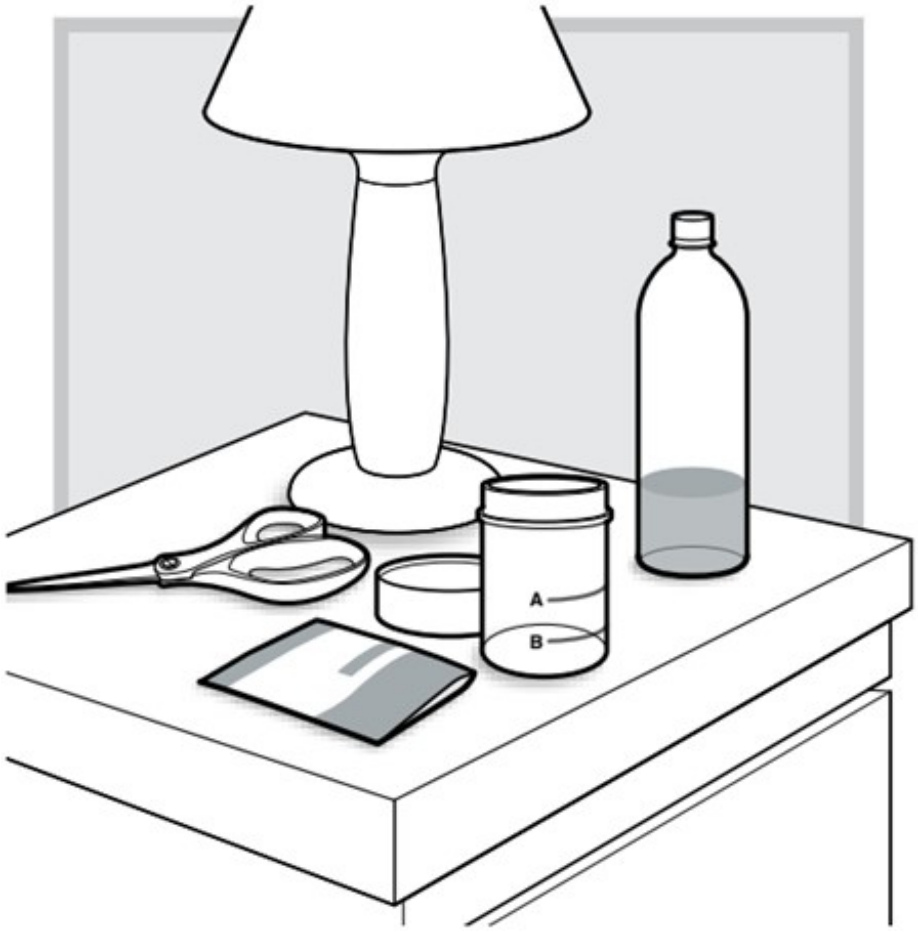
13.) Open the mixing cup by twisting the cap to the left (counter-clockwise) and remove it.

14.) Drink (or have your child drink) the mixed solution immediately after mixing.

Make sure you (or your child) drink all the mixed solution in the mixing cup.

15.) Leave the empty mixing cup at your (or your child's) bedside and immediately lie down (or have your child lie down) to go to sleep.

Avoid getting out of your bed (or having your child get out of bed) after taking LUMRYZ.

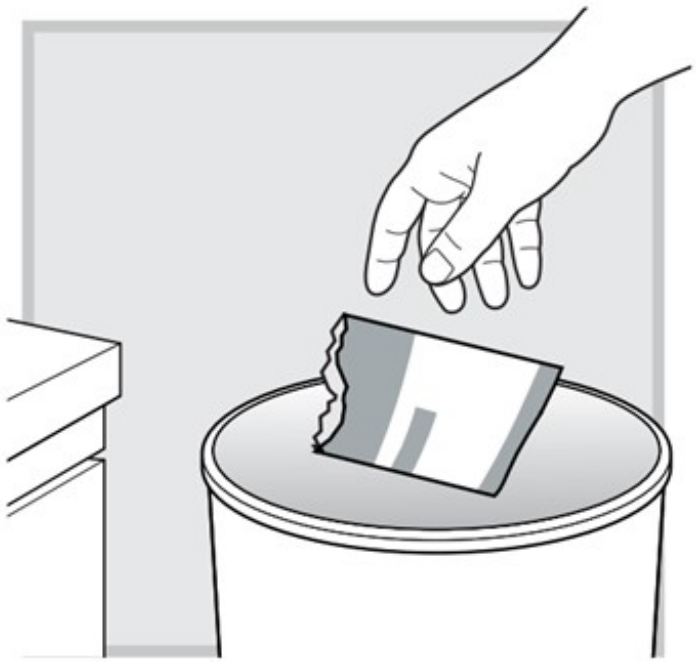


Continue to Step 16

How do I throw away (dispose of) LUMRYZ?

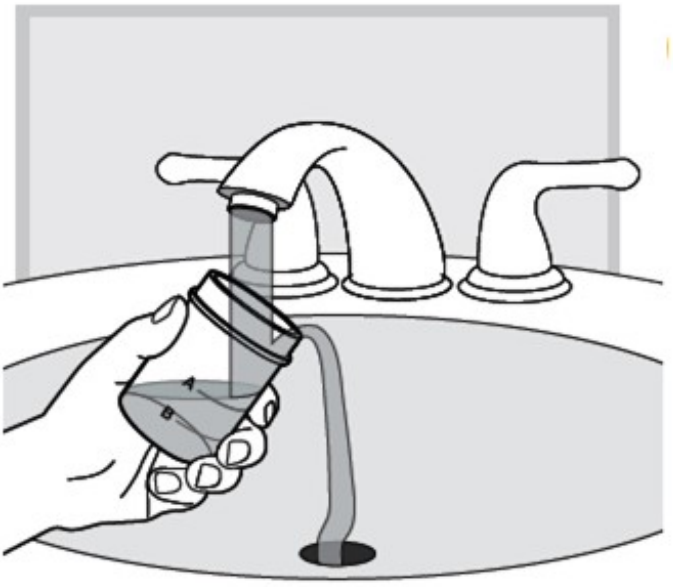
16.) The next day, place the empty LUMRYZ packet in the trash.

If any LUMRYZ remains in the packet, rinse it down the sink before (prior to) throwing away (disposal).



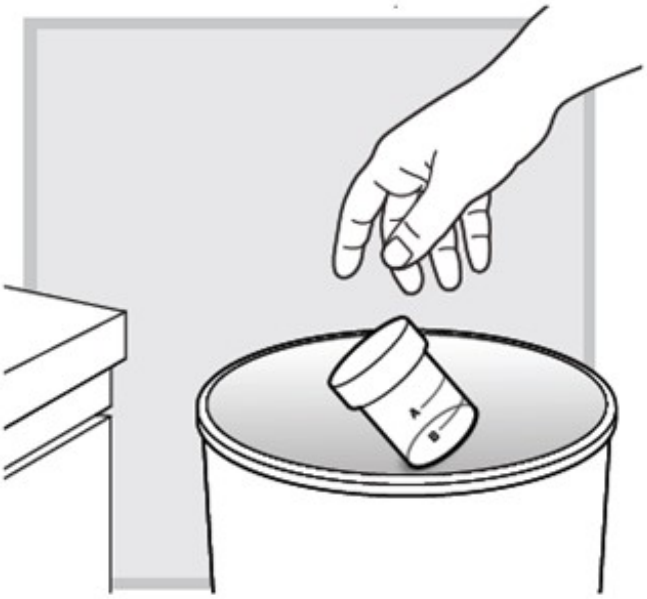
17.) Empty any unused LUMRYZ down the sink drain the next day.

Clean the mixing cup by rinsing it with water and letting it dry before each use.



After you (or your child) finish all of the packets in the LUMRYZ carton

After you have (or your child has) finished your (or your child's) last packet in the carton, throw away the rinsed mixing cup in the trash.



If you have additional questions about LUMRYZ, talk with your doctor.

You can also contact:
Alkermes, Inc
Waltham, MA 02451

For more information on LUMRYZ, visit **www.lumryz.com** or call 888-828-2335.

Lumryz (sodium oxybate) for extended-release oral suspension C-III **1 packet per dose**

Alkermes

Manufactured for:
Alkermes, Inc.
Waltham, MA 02451

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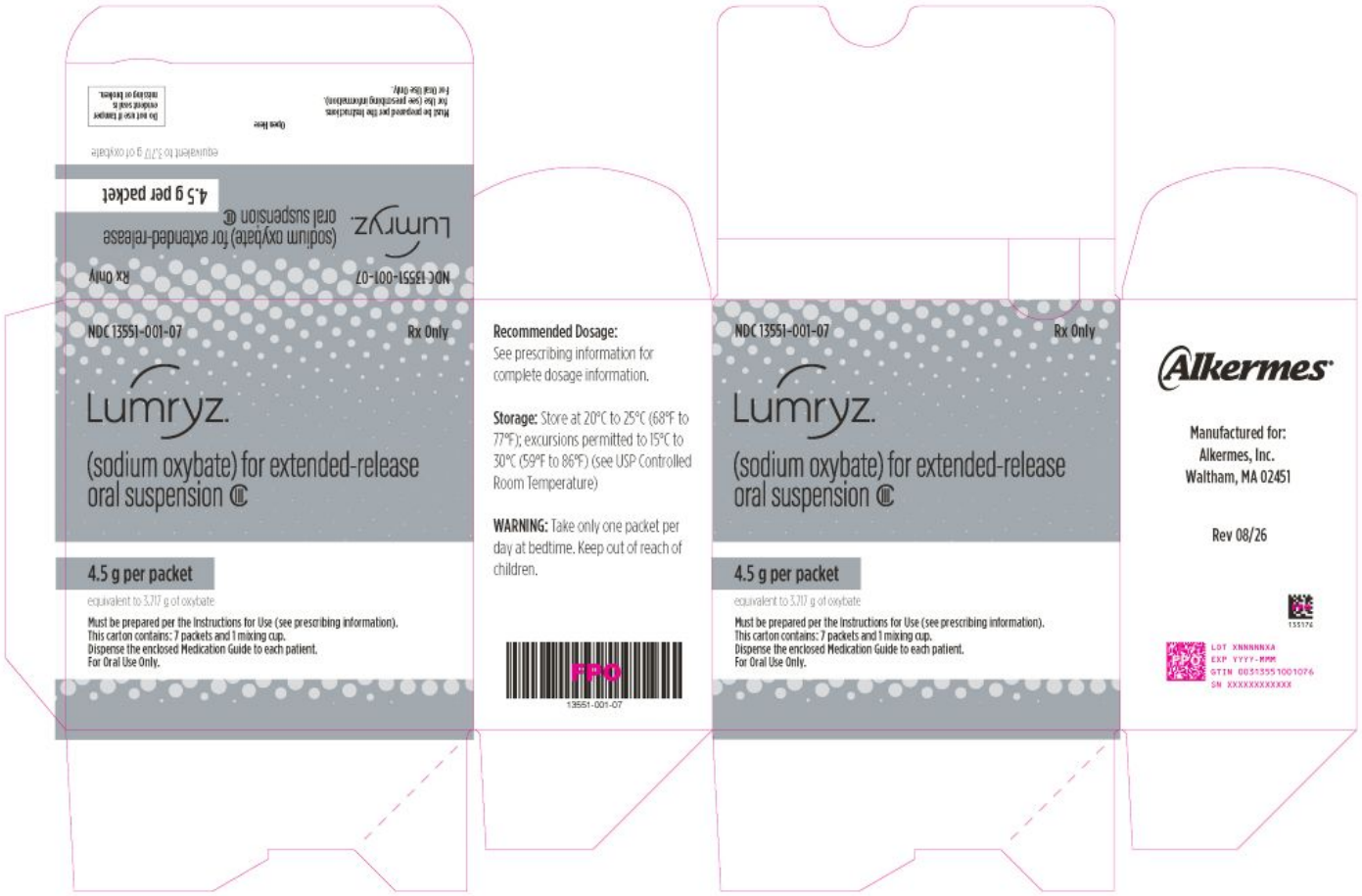
This Instructions for Use has been approved by the U.S. Food and Drug Administration.

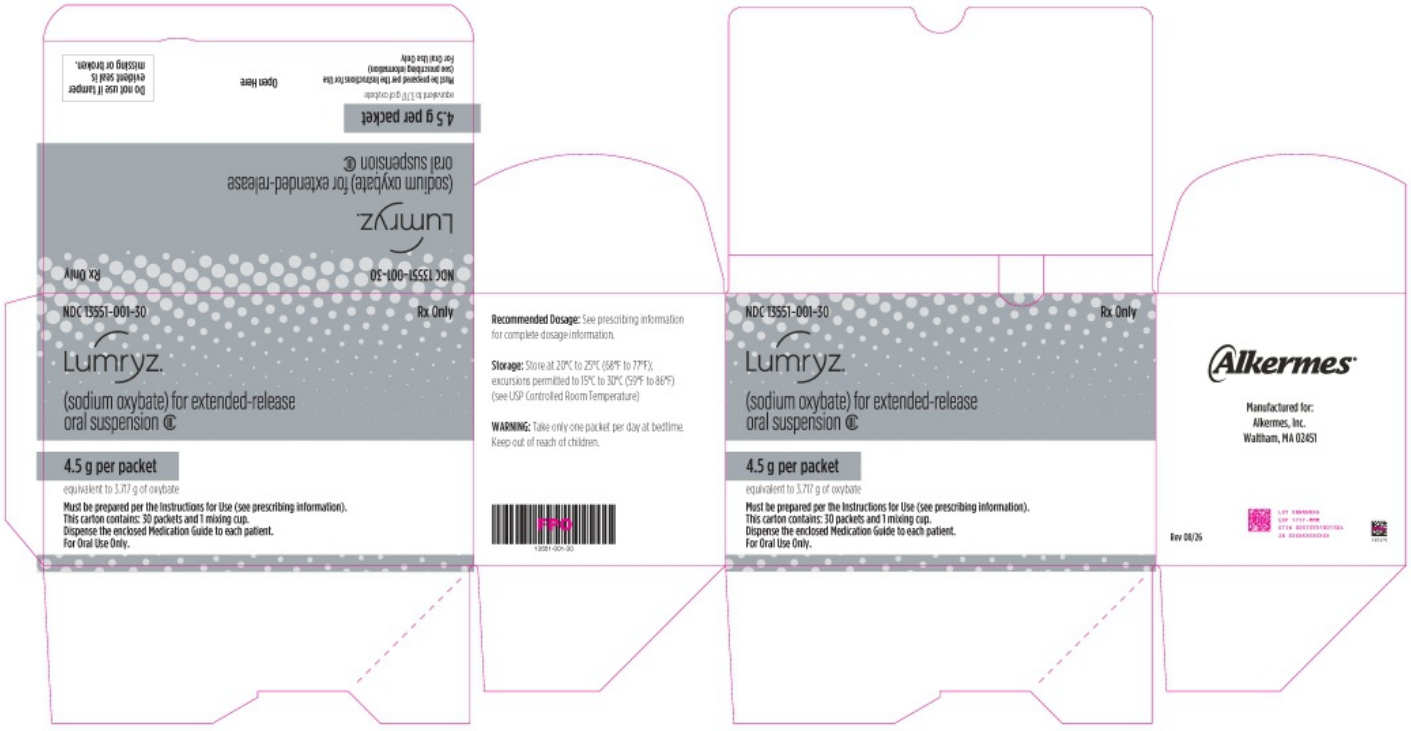
Revised: 08/2026

LUM-IFU:R4

PRINCIPAL DISPLAY PANEL - NDC: 13551-001-07 - 4.5 g 7-count Carton Label



PRINCIPAL DISPLAY PANEL - NDC: 13551-001-30 - 4.5 g 30-count Carton Label



PRINCIPAL DISPLAY PANEL - NDC: 13551-002-07 - 6 g 7-count Carton Label

PRINCIPAL DISPLAY PANEL - NDC: 13551-002-30 - 6 g 30-count Carton Label

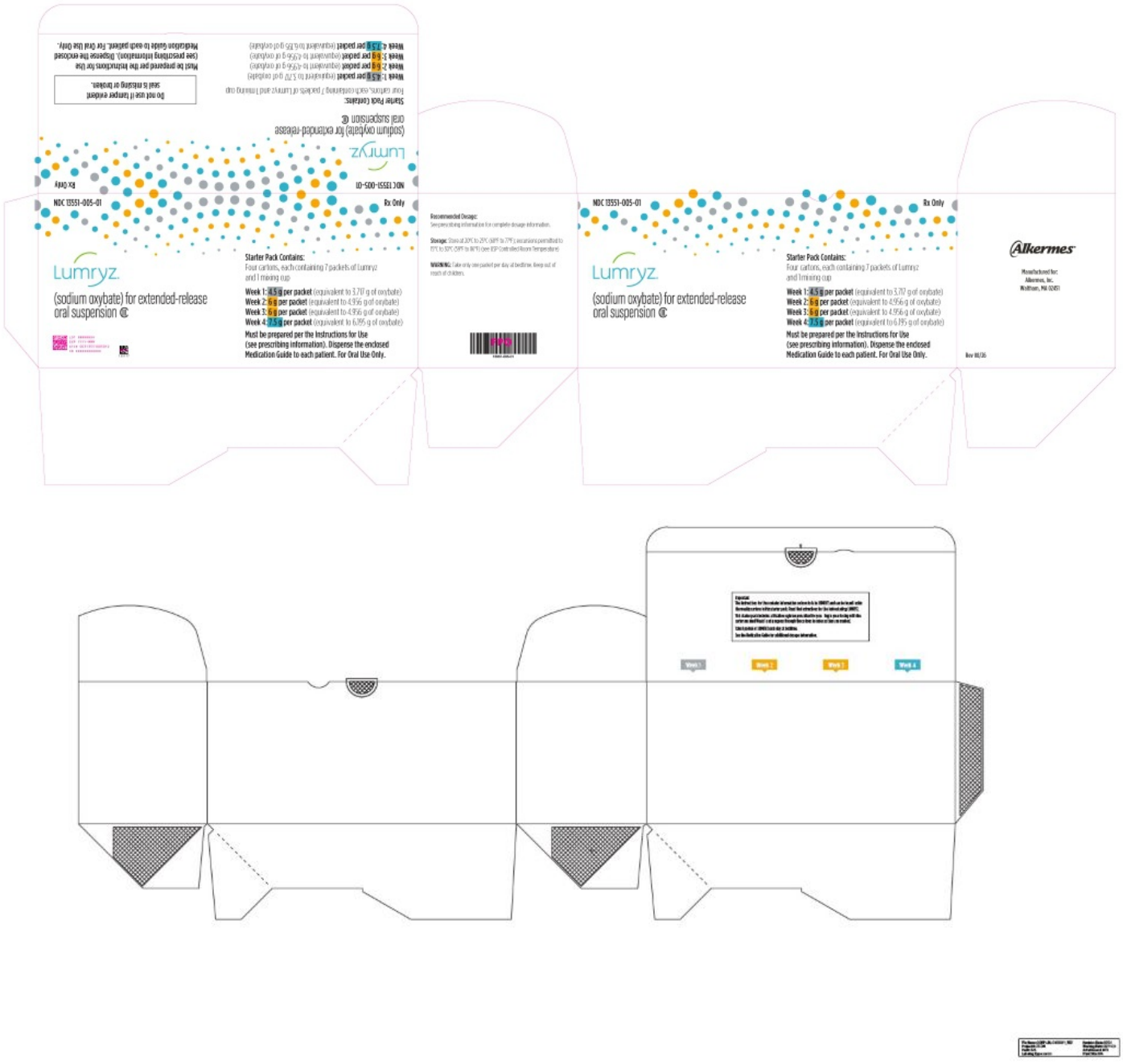
PRINCIPAL DISPLAY PANEL - NDC: 13551-003-07 - 7.5 g 7-count Carton Label

PRINCIPAL DISPLAY PANEL - NDC: 13551-003-30 - 7.5 g 30-count Carton Label

PRINCIPAL DISPLAY PANEL - NDC: 13551-004-07 - 9 g 7-count Carton Label

PRINCIPAL DISPLAY PANEL - NDC: 13551-004-30 - 9 g 30-count Carton Label

Principal Display Panel - NDC: 13551-005-01 - Starter Pack Outer Carton Label



LUMRYZ

sodium oxybate for suspension, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:13551-001
Route of Administration	ORAL	**DEA Schedule**	CIII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
SODIUM OXYBATE (UNII: 7G33012534) (4-HYDROXYBUTANOIC ACID - UNII:30IW36W5B2)	SODIUM OXYBATE	4.5 g

Product Characteristics			
Color	white (white to off-white powder)	**Score**	
Shape		**Size**	
Flavor		**Imprint Code**	
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:13551-001-07	7 in 1 CARTON	05/01/2023	
1		1 in 1 PACKET; Type 0: Not a Combination Product		
2	NDC:13551-001-30	30 in 1 CARTON	05/01/2023	
2		1 in 1 PACKET; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA214755	05/01/2023	

LUMRYZ

sodium oxybate for suspension, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:13551-002
Route of Administration	ORAL	**DEA Schedule**	CIII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
SODIUM OXYBATE (UNII: 7G33012534) (4-HYDROXYBUTANOIC ACID - UNII:30IW36W5B2)	SODIUM OXYBATE	6 g

Product Characteristics

Color	white (white to off-white powder)	**Score**	
Shape		**Size**	
Flavor		**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:13551-002-07	7 in 1 CARTON	05/01/2023	
1		1 in 1 PACKET; Type 0: Not a Combination Product		
2	NDC:13551-002-30	30 in 1 CARTON	05/01/2023	
2		1 in 1 PACKET; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA214755	05/01/2023	

LUMRYZ

sodium oxybate for suspension, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:13551-003
Route of Administration	ORAL	**DEA Schedule**	CIII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
SODIUM OXYBATE (UNII: 7G33012534) (4-HYDROXYBUTANOIC ACID - UNII:30IW36W5B2)	SODIUM OXYBATE	7.5 g

Product Characteristics

Color	white (white to off-white powder)	**Score**	
Shape		**Size**	
Flavor		**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:13551-003-07	7 in 1 CARTON	05/01/2023	
1		1 in 1 PACKET; Type 0: Not a Combination Product		
2	NDC:13551-003-30	30 in 1 CARTON	05/01/2023	
2		1 in 1 PACKET; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA214755	05/01/2023	

LUMRYZ

sodium oxybate for suspension, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:13551-004
Route of Administration	ORAL	**DEA Schedule**	CIII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
SODIUM OXYBATE (UNII: 7G33012534) (4-HYDROXYBUTANOIC ACID - UNII:30IW36W5B2)	SODIUM OXYBATE	9 g

Product Characteristics

Color	white (white to off-white powder)	**Score**	
Shape		**Size**	
Flavor		**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:13551-004-07	7 in 1 CARTON	05/01/2023	
1		1 in 1 PACKET; Type 0: Not a Combination Product		
2	NDC:13551-004-30	30 in 1 CARTON	05/01/2023	
2		1 in 1 PACKET; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA214755	05/01/2023	

LUMRYZ

sodium oxybate kit

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:13551-005
DEA Schedule	CIII		

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:13551-005-01	1 in 1 CARTON; Type 1: Convenience Kit of Co-Package	10/07/2024	

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	7 PACKET	7
Part 2	14 PACKET	14
Part 3	7 PACKET	7

Part 1 of 3

LUMRYZ

sodium oxybate for suspension, extended release

Product Information

Item Code (Source)	NDC:13551-001		
Route of Administration	ORAL	**DEA Schedule**	CIII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
SODIUM OXYBATE (UNII: 7G33012534) (4-HYDROXYBUTANOIC ACID - UNII:30IW36W5B2)	SODIUM OXYBATE	4.5 g

Product Characteristics			
Color	white (white to off-white powder)	**Score**	
Shape		**Size**	
Flavor		**Imprint Code**	
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1		1 in 1 PACKET; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA214755		

Part 2 of 3

LUMRYZ

sodium oxybate for suspension, extended release

Product Information			
Item Code (Source)	NDC:13551-002		
Route of Administration	ORAL	**DEA Schedule**	CIII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
SODIUM OXYBATE (UNII: 7G33012534) (4-HYDROXYBUTANOIC ACID - UNII:30IW36W5B2)	SODIUM OXYBATE	6 g

Product Characteristics			
Color	white (white to off-white powder)	**Score**	
Shape		**Size**	
Flavor		**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		1 in 1 PACKET; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA214755		

Part 3 of 3

LUMRYZ

sodium oxybate for suspension, extended release

Product Information

Item Code (Source)	NDC:13551-003		
Route of Administration	ORAL	**DEA Schedule**	CIII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
SODIUM OXYBATE (UNII: 7G33012534) (4-HYDROXYBUTANOIC ACID - UNII:30IW36W5B2)	SODIUM OXYBATE	7.5 g

Product Characteristics

Color	white (white to off-white powder)	**Score**	
Shape		**Size**	
Flavor		**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		1 in 1 PACKET; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA214755		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA214755	10/07/2024	

Labeler - Alkermes, Inc. (185481132)

Revised: 9/2026 Alkermes, Inc.